American Heart Journal

VOL. 31 MARCH, 1946 NO. 3

FRED M. SMITH
1888—1946

ON FEB. 23, 1946, Dr. Fred M. Smith died suddenly at his home in Iowa City. It is fitting that this public announcement of his death can be made in this JOURNAL, which until very recently he edited with great distinction.

Doctor Smith's death will bring a sense of sadness and regret to many persons: to those who knew him as a teacher, to those who knew him as a physician, and particularly to those who were privileged to know him as a friend.

Fred Smith's was a peculiarly full though short life: a life that hardly any conscientious physician can fail to envy. His contributions to medicine as a teacher, as a writer, and as an investigator were very substantial. He will be remembered for many reasons. Probably he will be best remembered for his contribution to our knowledge of the disease which finally claimed him and for his utter devotion to his profession, which in his code had higher precedence than his life.

Although this brief notice is being sponsored only by the American Heart Association, by the Editorial Board of the AMERICAN HEART JOURNAL, and by The C. V. Mosby Company, the sentiments which it expresses will be felt very poignantly by the many persons who came under the spell of Doctor Smith's influence. They will feel, as we feel, that American medicine has suffered a great loss.

Original Communications

A STUDY OF THE SUBJECTIVE SENSATIONS ASSOCIATED WITH EXTRASYSTOLES

EDWARD M. KLINE, M.D., CLEVELAND, OHIO, AND
LIEUTENANT (J.G.) THOMAS G. BIDDER, USNR

IT HAS been the general opinion that the subjective sensations sometimes associated with extrasystoles were produced by the first normal heartbeat following the compensatory pause. This beat is an unusually large one, owing to the increased filling of the heart during the long diastole. This explanation seemed so logical to the authors that no particular thought was given to other possible mechanisms until Ungerleider and Gubner[1] proposed that the sensations were due to the premature beat itself. White, referring to the symptoms associated with extrasystoles, writes, "Often, however, the occurrence of the premature beat is felt as a more or less disagreeable sensation, due less to the abnormal beat itself than to the pause which follows it, to the vigorous thump of the first normal beat after the pause, or to the pressure wave forced up into the neck veins from the right auricle at the time of the premature beat; this pressure wave results from the contraction of the auricles while the ventricles are in systole."[2]

In an effort to settle the matter conclusively it was decided to study individuals who experienced some type of subjective symptoms with their extrasystoles. Many persons were seen who had vague precordial sensations and extrasystoles, but in these patients there was no close association between the extrasystoles and the subjective complaints. Many more were completely unaware of their extrasystoles. Eleven individuals were found who were conscious of practically all extrasystoles, and, in these persons, 167 premature beats were studied as a basis for this report. In nine persons ventricular extrasystoles alone were present; in one, auricular extrasystoles alone were present; and in the remaining subject both types were present. These individuals were asked to press a signal key the instant they experienced their customary symptoms. This signal (*C* in all figures) was recorded with a simultaneous electrocardiogram (*D*), phonocardiogram (*B*), and radial pulse tracing (*E* in all figures except Fig. 3).*

From the Department of Medicine, Western Reserve University, and Lakeside Hospital, Cleveland, Ohio.

Read by title at the Seventeenth Annual Meeting of the Central Society for Clinical Research, Chicago, Nov. 3 and 4, 1944.

Received for publication June 14, 1945.

*For office testing without the aid of additional equipment, a simple arrangement can be worked out with any electrocardiograph. The machine is placed near enough to the patient so that his hand can rest comfortably on the standardization button. He then is instructed to press the button the instant he notices the sensation in his chest, and a record similar to that shown in Fig. 2, *F*, is obtained.

The subjects' reaction times were determined by tapping their precordia lightly with an instrument which recorded the time of contact (*A*, first deflection, all figures). The subjects then pressed a second button the instant they felt the instrument strike their chests (*A*, second deflection). The electrocardiograph was used to measure this interval, which was most often found to be about 0.2 second.

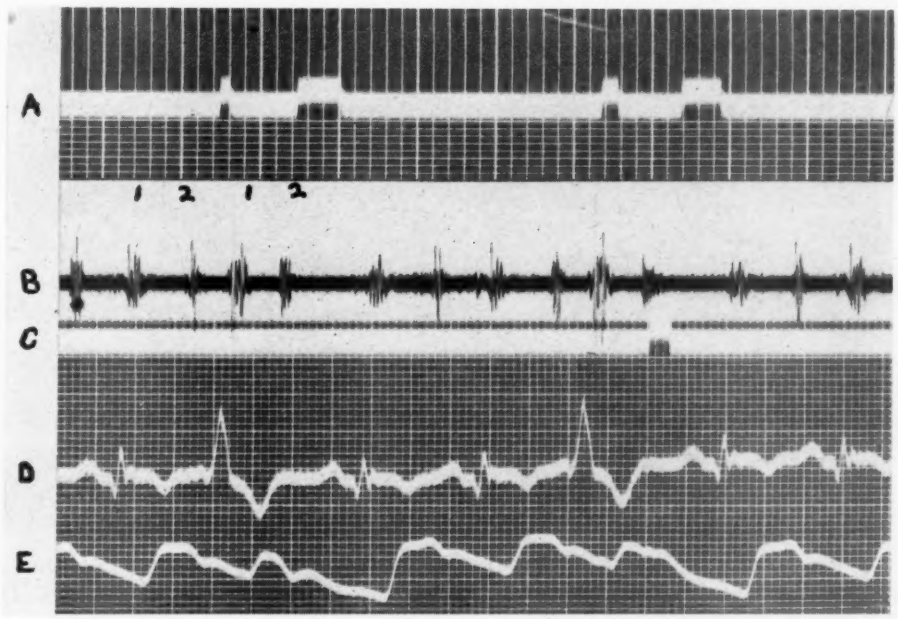


Fig. 1.—H. R. *A*, Test of reaction time. First deflection represents the contact of testing instrument with the precordium. The subject felt the contact and pressed the signal button at the time of the second deflection. Two tests are shown. *B*, Phonocardiogram. Note that the first sounds of the extrasystoles are louder than those of the normal beats. *C*, Signal indicating patient's awareness of extrasystoles. The first one was passed. *D*, Lead III; two ventricular extrasystoles are shown. *E*, Radial pulse tracing.

RESULTS

Our subjects reacted to the perception of their extrasystoles in a remarkably constant manner. This was unexpected; we had believed that we would get many types of reactions. Every subject pressed the signal key (*C* in all figures) during the pause after the premature beat (*D* in all figures) and before the appearance of the first normal beat. Therefore, it was not this unusually forceful beat after the pause that produced the symptoms, but rather either the premature beat itself or the compensatory pause which followed the premature beat.

There is nothing in our data to support the view that it is the pause that one notices. By inspection of the figures it can be seen that in each instance, the signal (*C*) was given considerably in advance of the time when the next normal beat was due. For example, in Fig. 1 the average R-R interval measures 0.60 second. The signal was given 0.32 second after the R wave of the second

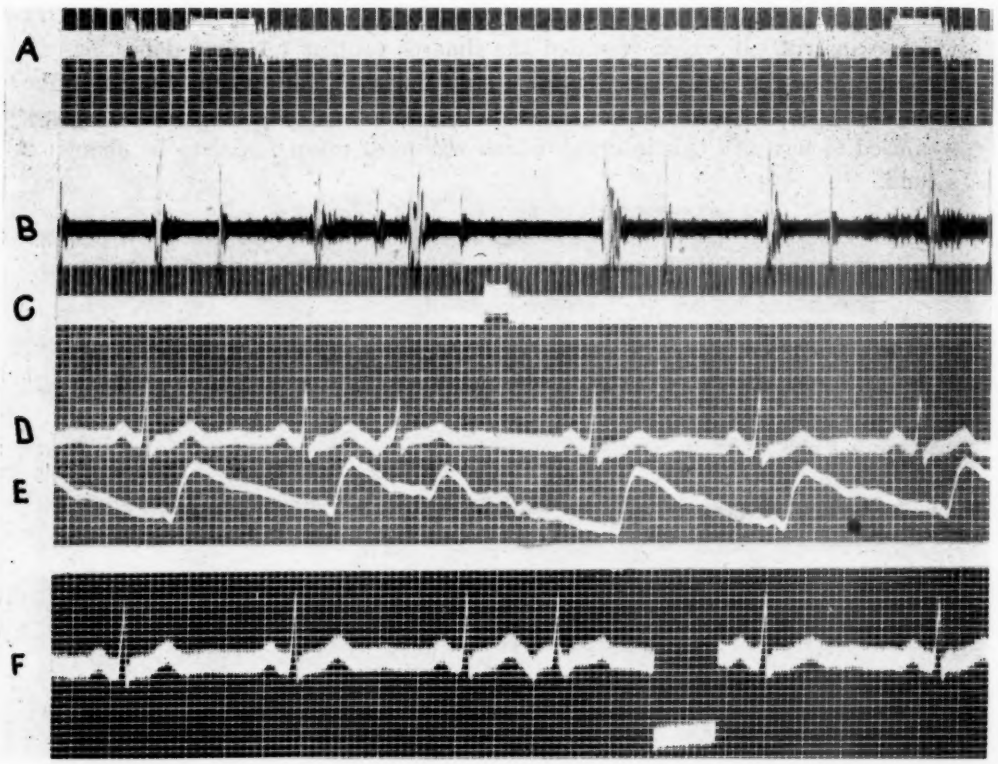


Fig. 2.—W. J. *A*, Test of reaction time. *B*, Phonocardiogram. *C*, Signal indicating subject's awareness of extrasystoles. *D*, Lead II; one auricular extrasystole is shown. *E*, Radial pulse tracing. *F*, Subject pressed electrocardiograph standardization button when extrasystole was noticed. Lead II; one auricular extrasystole is shown.

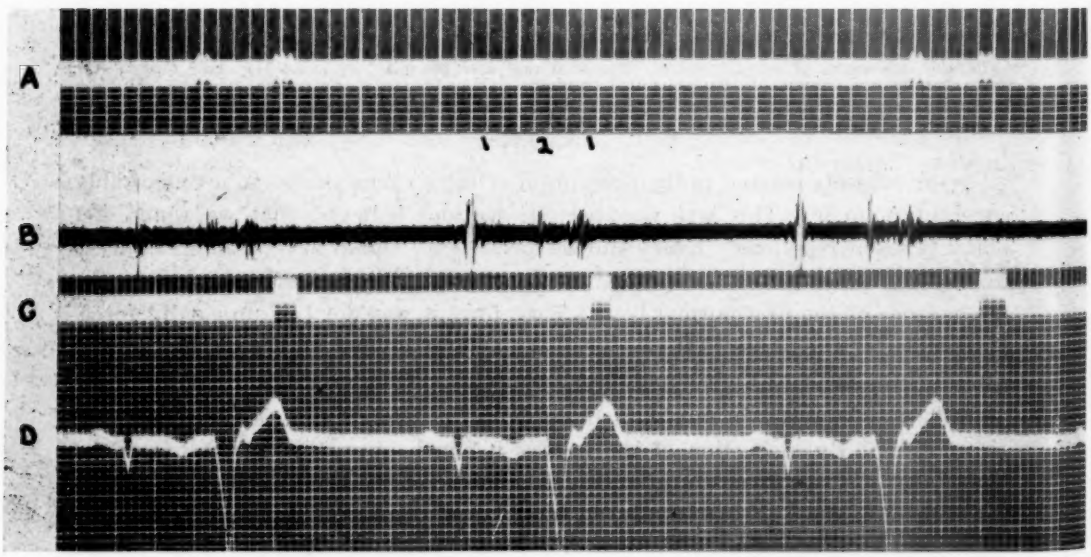


Fig. 3.—A. W. *A*, Test of reaction time. *B*, Phonocardiogram. Note that the first sounds of the extrasystoles are of smaller volume than those of the normal beats. *C*, Signal indicating subject's awareness of extrasystoles. *D*, Lead III, ventricular extrasystoles producing a bigeminal rhythm.

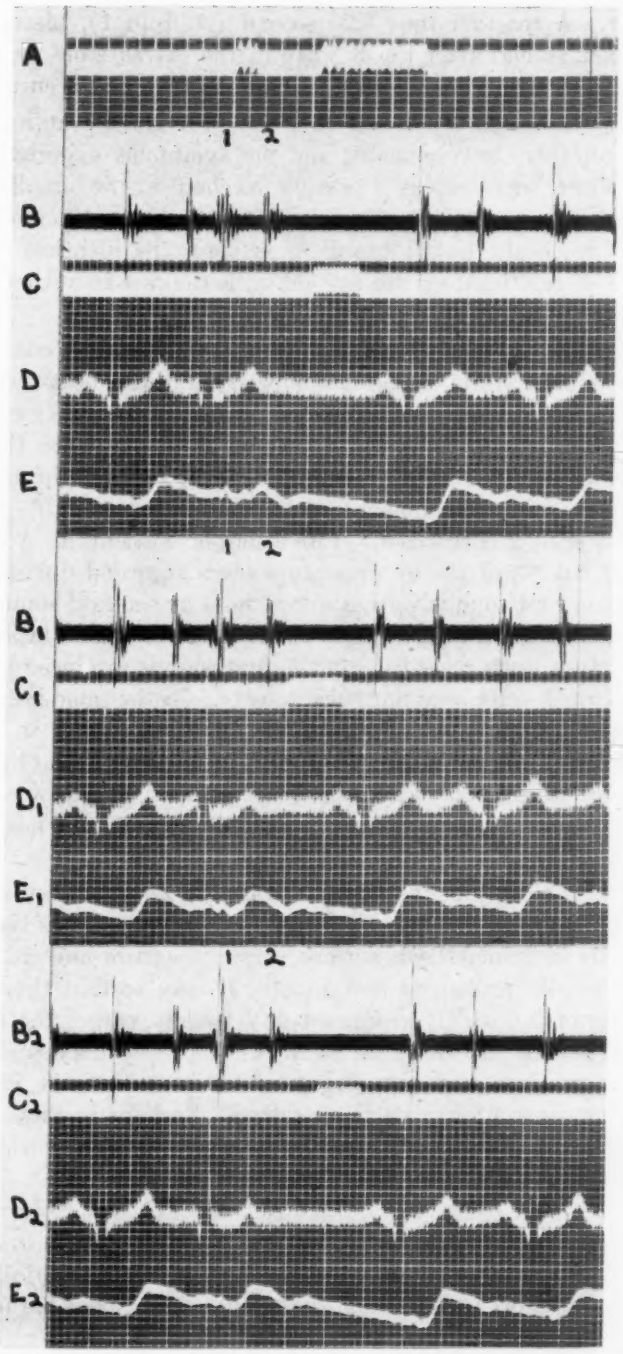


Fig. 4.—G. B. *A*, Test of reaction time. *B*, Phonocardiogram. Note that the first sound of the extrasystole is reduced in volume. B_1, In the case of this extrasystole the first sound is of about equal intensity to that of the normal beats. B_2, The first sound of this extrasystole is definitely increased in intensity. *C*, C_1 and C_2, Signal indicating subject's awareness of extrasystoles. *D*, D_1 and D_2, Lead II; ventricular extrasystoles. *E*, E_1 and E_2, Radial pulse tracing.

premature beat. A reaction time 0.20 second (*A*, Fig. 1), places the time of perception at 0.12 second after the R wave of the extrasystole, and 0.48 second before the next beat would have been due if the rhythm had been uninterrupted.

It is clearly indicated, then that it is the premature beat itself which, by one means or another, is responsible for the symptoms experienced by these individuals. White[2] mentions as a possible mechanism the simultaneous occurrence of auricular and ventricular systole. This might be a factor in some ventricular premature beats, but it could not explain the identical response of a person whose A-V relationships are normal, as is the case in auricular premature beats (Fig. 2).

Ungerleider and Gubner[1] found that in persons who were conscious of their extrasystoles the first heart sound accompanying these beats was invariably louder than the first sound of the normal beats. This increased intensity is what one would anticipate when systole occurs at a time when the A-V valves are widely separated, particularly since the snapping shut of these valves is responsible for the major component of the first heart sound.[3] We, however, could not make such a correlation. For example, Patient A. W. (Fig. 3) was conscious of all but six of the 67 premature beats recorded during the test, yet the accompanying first sounds were never so loud as the first sounds of the normal beats. On the other hand, Patient H. R. (Fig. 1) was conscious of only 20 of the 56 premature beats recorded, yet the first sounds produced by these extrasystoles were always well above normal intensity. In the same individual, variations in volume of the first sounds caused no apparent change in the subjective sensations that these extrasystoles produced. In patient G. B. (Fig. 4) the first sound of the premature beat is of decreased intensity in *B*, of equal intensity in B_1, and of increased intensity in B_2; yet this patient did not fail to notice any of the 19 premature beats recorded during the test.

Although it is clear that the premature beat is responsible for the symptom of palpitation, no adequate explanation for the mechanism has been found. In some individuals in whom the beats are very premature and are accompanied by loud or unusually prolonged first sounds, it may be that this sound, or the vigorous closing of the widely separated A-V leaflets, causes the disturbance to reach conscious levels. On the other hand, when prematurity is slight, often no more than one sees in a moderate degree of sinus arrhythmia, it is difficult to imagine that the same mechanism is operating. Perhaps in these cases it is the unusual relationship of auricular and ventricular systoles, which sometimes occur simultaneously, that produces the symptoms.

SUMMARY

1. Eleven individuals with extrasystoles and associated subjective sensations were studied in an effort to determine the mechanism responsible for their symptoms.

2. Without exception it was found that the premature beat produced the subjective sensation.

3. In certain instances, when the premature beat occurred during the period of rapid ventricular filling, the symptoms may have resulted from the forceful closing of the A-V valves. In other situations this mechanism does not explain the observations recorded.

REFERENCES

1. Ungerleider, H. E., and Gubner, R. S.: Extrasystoles and the Mechanism of Palpitation, Tr. Am. Therap. Soc. **42:** 169, 1942.
2. White, P. D.: Heart Disease, New York, 1944, The Macmillan Co., p. 858.
3. Lewis, J. K., and Dock, W.: Origin of Heart Sounds and Their Variations in Myocardial Disease, J. A. M. A. **110:** 271, 1938.

TREATMENT OF CORONARY DISEASE WITH ANGINA BY PERICORONARY NEURECTOMY COMBINED WITH LIGATION OF THE GREAT CARDIAC VEIN

A Case Report

Mercier Fauteux, M.D.
Boston, Mass.

IT IS well known that in coronary disease sensory disturbances, vasomotor reactions, and mechanical interferences with the coronary blood flow are always intimately interwoven. It is probable that a single group of these pathologic phenomena never acts alone. Surgical operations so far developed for the treatment of coronary artery disease have as their specific objective only the abolition of some reflexes or the correction of some mechanical disturbances of the blood supply to the heart and have not been designed to attack all these abnormal conditions.

No operation which fails to abolish all of these disequilibria can possibly bring about satisfactory and permanent results in the treatment of coronary disease. Operations of such limited scope produce only partial or temporary improvement and do not affect the general aspect or course of the disease. It is no wonder that most of the operations devised have not stood the test of time and are no longer used.

The object of all our experimental studies has been to develop a procedure which would eradicate sensory disturbances, vasomotor reactions, and mechanical circulatory disorders. Because arteriosclerotic disease of the coronary arteries is similar to that of the extremities, it was assumed that surgical methods used in the treatment of peripheral vascular disease could be applied to coronary disease.

Leriche, in 1917, advanced the idea that partial arteriectomy could have value in the treatment of some forms of arteritis. He developed this theory in more detail at the French Surgical Convention in 1922, and has elaborated on it since.[1-6] In his opinion, the resection of a major diseased arterial trunk interrupts vasoconstrictive pathways and invariably brings about an active vasodilatation. His experimental studies and results seem to substantiate his views. So impressed was he with the beneficial and permanent results of partial arteriectomy in the extremities that he went so far as to suggest it as a worthwhile procedure in coronary disease.

In 1913, Oppel[7] demonstrated the efficacy of ligating the popliteal vein in the treatment of senile gangrene of the foot. Since then others have confirmed his work. In 1937, Gross, Blum, and Silverman[8] reported experiments showing

Laboratory for Surgical Research, Harvard Medical School, and The Peter Bent Brigham Hospital, Boston, Massachusetts.
Received for publication April 2, 1945.

that occlusion of the coronary sinus in the dog increased the blood supply and reduced the incidence of infarction following ligation of the coronary artery. The author has reported the results of his studies on the effects of both arteriectomy and venous ligation on the dog's heart.[9-11] Partial coronary arteriectomy was found incompatible with life in dogs with normal coronaries. However, when this procedure was combined with coronary venous ligation, the mortality rate was considerably lower. It was concluded that ligation of the great cardiac vein after occlusion of the anterior descending branch of the left coronary artery of the dog helps to maintain adequate coronary circulation after partial coronary arteriectomy. Later, in other experiments (unpublished), a segment of the coronary artery was rendered chronically inflamed. Resection of this modified arterial segment was compatible with life in many instances. Moreover, the incidence of infarction was diminished. Such a procedure has no possible application to clinical cases, as it is impossible to secure coronograms* in man to demonstrate accurately which arterial segment should be resected.

LIGATION OF THE GREAT CORONARY VEIN IN MAN

Although it was realized that coronary venous ligation could do no more than hasten the development of the coronary anastomotic system, the experimental results of coronary venous ligation were so encouraging that it was decided to ligate the great cardiac vein in a carefully selected group of patients in order to determine the value of this surgical procedure for man.

The first patient was operated on in 1939.[12] Since then nine other patients have received the same treatment. A complete study of the final results of their operations was presented before the New England Heart Association in March, 1943. All these patients had a history of coronary thrombosis which was confirmed by electrocardiographic tracings. Some of them gave a history of two attacks of coronary thrombosis. All of them were practically disabled by "angina of effort" and did not respond to rest and medication.

Only one patient died postoperatively. A tear in the pleura occurred while the heart was being exposed. In spite of careful suturing of this tear, the patient died approximately one hour after operation. Pneumothorax under tension was found at autopsy. Nothing else was found to explain the death of the patient.

A 65-year-old patient recovered well from the operation and was discharged from the hospital relieved of his pain. He died from progressive myocardial failure three months after operation. At autopsy the findings were general arteriosclerosis, coronary sclerosis with marked narrowing of the lumen, myocardial fibrosis, and recent infarction of the left kidney. Because this patient had given evidence of cardiac failure preoperatively, he was obviously a poor candidate for coronary venous ligation.

The first patient, operated on in 1939, died suddenly two and one-half years later. Before operation, he was not able to walk one block without developing dyspnea. The slightest emotional upset provoked substantial pain.

*This term applies to the visualization of the coronary arteries by x-ray films.

Five months after operation, he walked five miles without resting and had no discomfort. He resumed his work as a janitor. Frequent examinations up until the time of his death showed that the marked improvement in his condition noticed after venous ligation was maintained. At necropsy there were no adhesions between the pleura and the chest wall. The external surface of the pericardium was smooth and covered by a thick layer of fat reaching the aortic arch and projecting laterally on each side of the heart. The pericardium was slightly thicker than normal. The heart weighed 620 grams. The ramus descendens was occluded 2.5 cm. from its origin and was atheromatous and stenosed throughout its course. The circumflex artery was occluded 5 mm. beyond the bifurcation of the left coronary trunk. The right coronary artery was patent, slightly stenosed, and slightly atheromatous. The left ventricle was dilated;

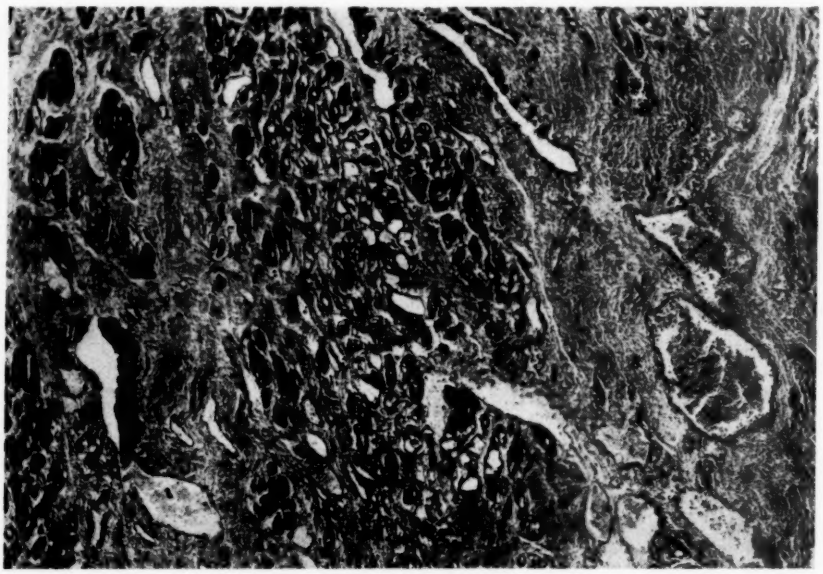


Fig. 1.—Photomicrograph of heart muscle of patient operated on April 19, 1939, showing a high degree of vascularity.

there was no aneurysm. No evidence of old or recent infarction of important size was found. Histologic sections showed a high degree of vascularity of the cardiac muscle. The blood vessels of the posterior and anterior papillary muscles were markedly dilated and gave the appearance of being cavernous. Actual pools of blood were also found in the sections examined (Fig. 1).

Of this series of nine patients, seven are still alive: three of them five years after operation and four of them four years after operation. All seven patients have resumed their work and are able to enjoy life. Although one complained of anginal pain, yet he resumed the occupation which he had had to abandon prior to operation. The others have also returned to the same type of work in which they were engaged before coronary disease incapacitated them and have complained of only slight and infrequent discomfort appearing at the end of a

day's work. Two patients, however, when they are fatigued, have a sensation of pressure without pain over the precordial area.

The experience gained from this small series of cases is of considerable value. The following deductions can be made: (1) The operative mortality was low. The complication which caused death in one patient might have been avoided. (2) The effects of venous ligation on the vascularity of the heart could be carefully studied in the patient who lived over two and one-half years after operation. The histologic sections demonstrated that venous ligation in the heart produces the same results that it does in the extremities. It opens and dilates coronary anastomoses. This anastomotic improvement is not only an immediate and transitory effect but apparently a permanent one. (3) The fact that all the patients who survived were able to resume their work, most of them without discomfort, seems to indicate that coronary venous ligation effects the natural development of collateral circulation and improves both the nutrition of the heart and its functional capacity. This seems about all that one should expect from this surgical procedure.

The coronary nervous system is not modified by this operation. Coronary reflexes, therefore, can still interfere with the function of the heart in different ways; for example, by provoking pain, by producing transitory ischemic myocardial states, and even by contributing to the initiation of ventricular fibrillation and sudden death. These pathologic phenomena were observed to a greater or lesser degree in some of our patients even after operation. It seemed plausible, therefore, that disruption of these reflexes would be beneficial to the patient with coronary disease.

PERICORONARY NEURECTOMY

To abolish or at least diminish substantially the incidence of reflexes resulting from stimulation of the nerve endings of the coronary arteries it was thought feasible to destroy most of the nerve branches reaching or leaving the left and right coronary arteries, since these branches are localized behind the pulmonary artery as well as in the nerve plexus over the ascending aorta. As nerve resection of this sort interrupts sympathetic, vagal, and sensory branches, it was called "pericoronary neurectomy." Experimental studies extending over a period of two years have been carried out by the author[13] in the Laboratory for Surgical Research at the Harvard Medical School. These studies will soon be reported in detail.

Briefly the results were as follows: In one group of dogs, the circumflex artery was ligated at its origin, that is, approximately 4 to 6 mm. from the aortic opening of the left coronary artery. Twenty per cent of these dogs survived. In the second group, which was prepared in advance by coronary venous ligation, the circumflex artery was ligated at the same level as in the control series. Forty per cent of this group lived. In the third group, prepared in advance by pericoronary neurectomy, ligation of the circumflex was done as in the previous groups. Sixty per cent survived. In the fourth group, prepared in advance by pericoronary neurectomy and coronary venous ligation, the circumflex artery was again ligated as in the previous groups. The survival rate

rose to 86.7 per cent. A fifth group* was prepared by pericoronary neurectomy and coronary venous ligation. Approximately one month after operation, the ramus descendens was occluded while the animals were conscious. Eighty per cent gave no indications of pain; in the remaining 20 per cent the responses were doubtful, but never the typical responses of the control series.

REPORT OF A CASE

These experimental findings suggested that pericoronary neurectomy with ligation of the great cardiac vein would be of greater value in the treatment of coronary disease than venous ligation alone. On Sept. 11, 1944, the first complete denervation of the left coronary artery in man was performed at the Peter Bent Brigham Hospital. Although the final results remain to be seen in this patient, it was thought that a report of this case would be of interest.

The patient, a 45-year-old painter, was admitted to the Surgical Service of the Peter Bent Brigham Hospital on July 27, 1944. One year before admission, he experienced, after exertion, three or four attacks of severe substernal pain which lasted three to four minutes each. He had no further trouble until three and one-half months before admission, when he noticed that walking uphill for a few minutes would bring on an attack of severe, aching substernal pain which radiated to the back and was accompanied by a sensation of numbness in the left upper arm. The pain came on suddenly and was relieved by rest. Frequently the attacks of pain were accompanied by nausea, but he never vomited. Such an attack never occurred while he was at rest.

An electrocardiogram was taken on June 19, 1944, in the Outpatient Department of the Peter Bent Brigham Hospital. It was reported to show left axis deviation and an abnormal Lead IV. A 7-foot heart film showed the heart to be only 4 per cent above normal in size. Fluoroscopy showed nothing remarkable. The physical examination was negative. A diagnosis of coronary disease and angina pectoris was made. Nitroglycerin was prescribed and gave some relief. One week before admission, the patient experienced an attack of pain which was similar to the previous attacks except that it occurred while he was resting in bed. He sat up in bed all night, as that seemed the only position in which he could tolerate the pain. He had no difficulty in breathing. The pain persisted for the next two days and was so severe that he could not rest. On the third day the pain disappeared. During his hospitalization he had several more brief attacks of substernal pain. These attacks occurred both at rest and after meals.

On examination, the patient was found to be a well-developed, rather thickset man whose nutrition was good. Apart from the cardiovascular system, the results of the examination were essentially negative. On admission, the temperature was 99.2° F.; the pulse, 104; and the respirations, 18. The white count was 8,400, and the blood pressure was 120/80. The apex impulse was neither seen nor felt. By percussion the left border of cardiac dullness was found at the midclavicular line and the right border 4.5 cm. from the midsternal line.

*Report to be published by Drs. Orvar Swenson and Mercier Fauteux.

Heart sounds were distant and a faint apical systolic murmur was present. The rhythm was regular.

Dr. Samuel A. Levine examined the patient and concluded that he had had a coronary thrombosis ten days before admission to the hospital. He advised bed rest, observation for six weeks, and re-evaluation after that period of time.

An electrocardiogram taken on July 28, 1944, showed left axis deviation, diphasic T waves in Lead I, and a normal Lead IV. The heart rate was 63 per minute; the P-R intervals were 0.16 second; and the QRS complexes were 0.08 second in duration (Fig. 2). The patient was kept in bed. He had only occasional attacks of angina and these gradually disappeared. On Aug. 14, 1944, he was allowed to leave his bed for the first time. Walking around the ward did not seem to trouble him. On Aug. 21, 1944, a two-stair exercise tolerance test performed by Dr. J. E. F. Riseman showed that 28 trips could be made before pain was initiated.

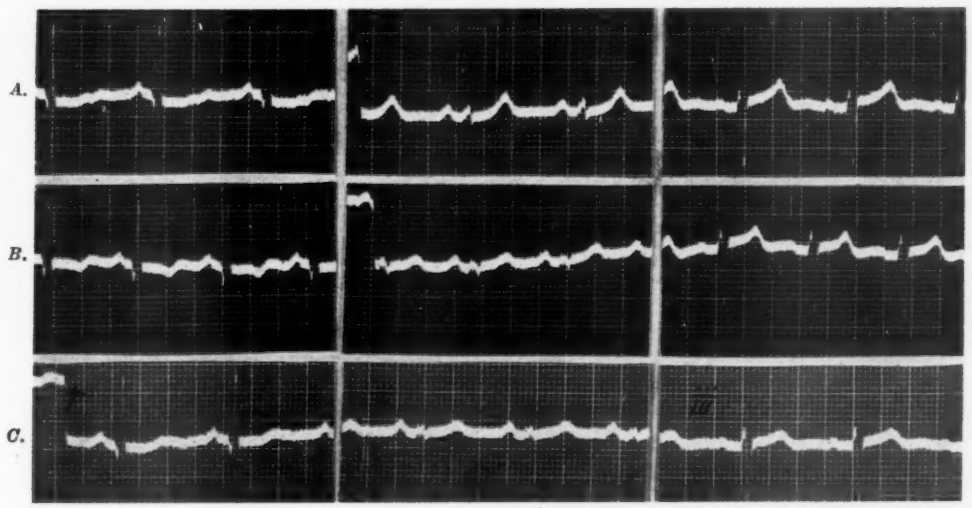


Fig. 2.—Electrocardiograms made before operation: *A*, July 28, 1944; *B*, Aug. 17, 1944; *C*, Aug. 28, 1944. Somewhat inverted T waves in Lead I and left axis deviation.

An electrocardiogram taken on Aug. 28, 1944, showed a normal Lead IV, a rate of 79 per minute; P-R intervals of 0.12 second; and QRS complexes of 0.08 second in duration (Fig. 2). The circulation time varied from 37 to 12 seconds. The vital capacity was 3,500 cubic centimeters.

On Sept. 11, 1944, pericoronary neurectomy combined with ligation of the great cardiac vein was performed under ether anesthesia with the assistance of Drs. Orvar Swenson and Charles A. Hufnagel. No special preoperative medication was administered. A right-angle incision was made, beginning at the level of the second left rib, curving over the right side of the midsternum and then going straight down approximately to the xiphoid. The second, third, and fourth left ribs as well as part of the sternum at this level were partially

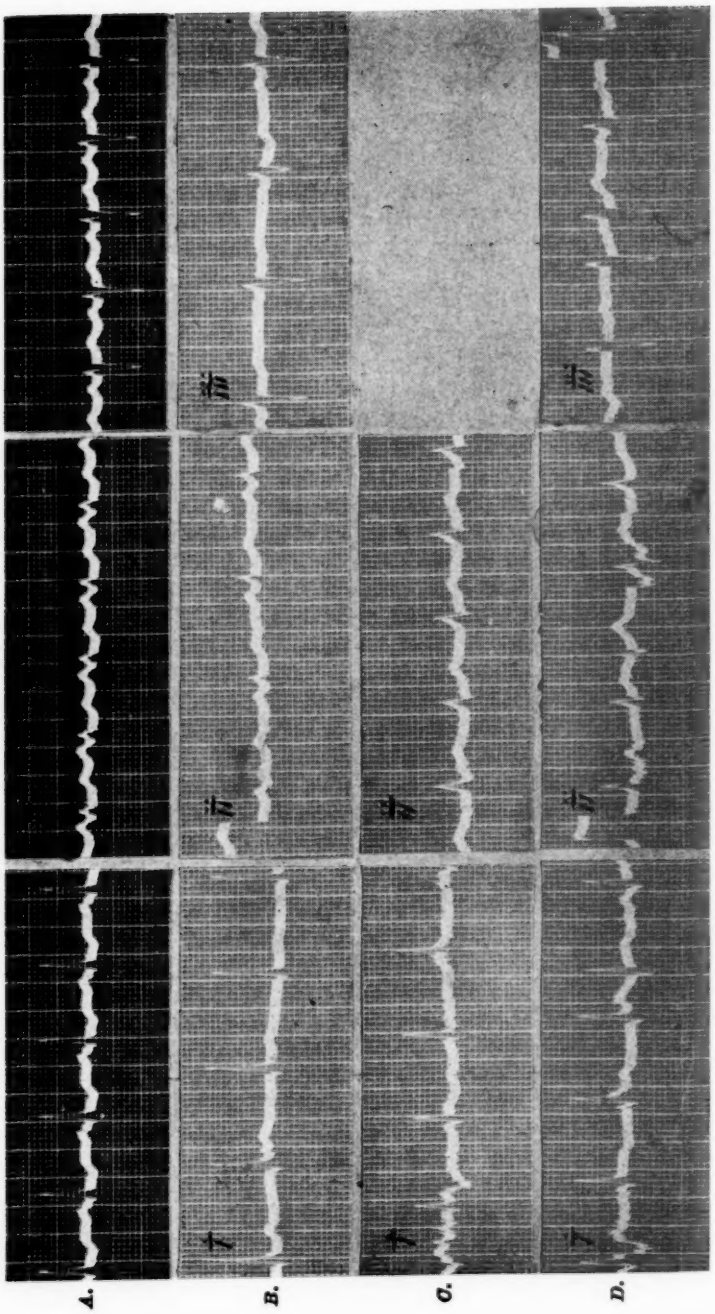


Fig. 3.—Electrocardiograms made at the time of operation. *A* was made after anesthetization but before incision. It is essentially the same as in Fig. 2. *B* was made during temporary venous occlusion. T_1 is slightly upright. *C* was made during pericoronary neurectomy. Lead I shows artifacts probably from manipulations. Lead II shows arrhythmia due to shifting pacemaker in A-V node. Lead III was not taken. *D* was made after phenolization. Artifacts appear in Lead I. Leads II and III show arrhythmia.

resected. With blunt gauze dissection, the pleura and left lung were gradually pushed laterally so as to give access to the cardiac area. The pericardium was incised vertically and then transversally. After exposure of the heart, the great cardiac vein was freed just below the origin of the coronary sinus. A ligature was passed under the vein, and both ends of the thread were crossed temporarily in order to observe the effects of coronary venous occlusion on the heart. Since this procedure did not produce any abnormalities in the blood pressure, pulse rate, or electrocardiogram (Fig. 3, *B*), the level of obstruction was considered satisfactory. The vein was not tied immediately because this would have caused troublesome distention of small venules in the field of the pericoronary neurectomy.

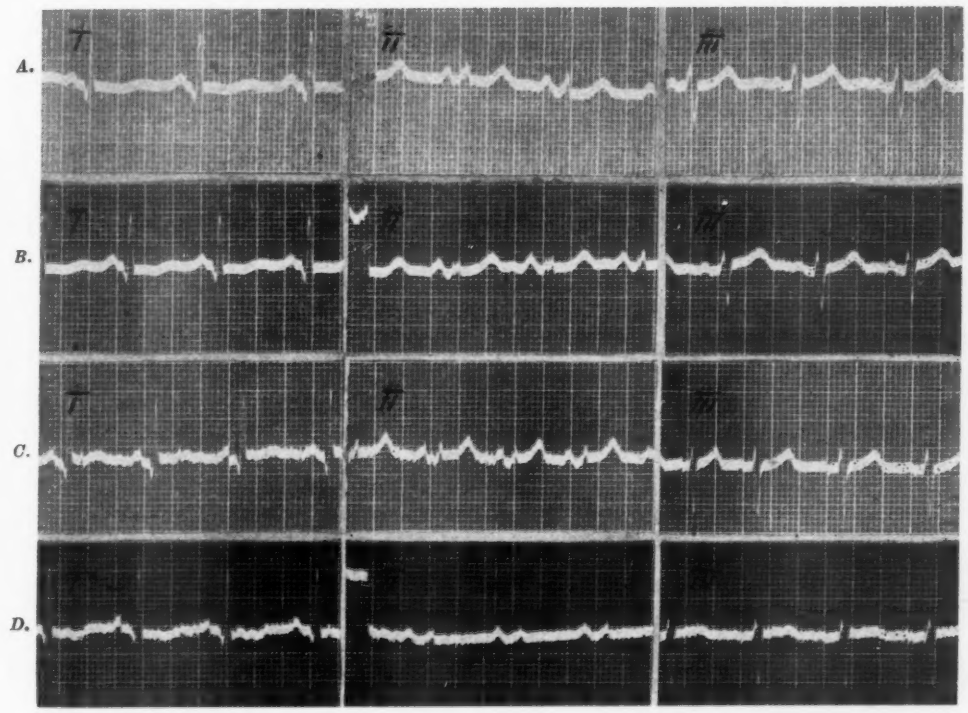


Fig. 4.—Electrocardiograms made after operation: *A*, immediately after operation; *B*, one hour and twenty minutes after operation; *C*, twenty-four hours after operation; and *D*, thirty-six days after operation.

The pulmonary artery was freed from the aorta and reflected to the right to expose the origin of the left coronary artery and the plexus between the aorta and pulmonary artery. The epicardial tissue over the left coronary artery was incised and resected down to a few millimeters below the bifurcation of the main trunk. Nerves emerging from behind the pulmonary artery and coursing toward either the main trunk of the left coronary artery or the ramus descendens were exposed and resected. Likewise the nerve branches merging from the left side of the aorta and reaching the left coronary main trunk or the origin of the circumflex branch were exposed and resected. During this procedure, the areas

exposed were frequently touched with small pieces of cotton soaked in novocain solution (2 per cent). Then the left coronary main trunk and the proximal part of both circumflex and ramus descendens branches were phenolized. During all these maneuvers, the heart behaved normally. There was hemorrhage, except for an insignificant oozing from the fat tissues covering the artery which was rapidly and easily controlled by application of fibrin foam. The electrocardiographic changes during operation were neither marked nor important (Fig. 3). A shifting pacemaker with the impulse starting sometimes high up, and sometimes low down in the A-V node which occurred during the dissection of the vein (Fig. 3, *C*); occasional ventricular extrasystoles at the beginning of the operation on the heart; bradycardia after ligation of the great cardiac vein. It should be stressed that the tracings obtained during and after dissection of perivascular nerve endings do not show significant changes in the T waves or in the S-T intervals.

The great cardiac vein was ligated. The pericardium was not sutured. The chest wound was closed without drainage. At the end of the operation, the patient was doing well (Fig. 4).

Postoperative Course.—Immediately after operation, oxygen was administered continuously for approximately four hours and then discontinued. Two days after operation, the patient was sitting up in a chair. On September 17, stitches were removed. The wound was normal. The patient progressed well until September 20, when he complained of tenderness of the calf of the left leg. He had a positive Homans' sign (pain in the calf on forced dorsiflexion of the foot). It was believed that the patient had thrombophlebitis. Bilateral femoral vein ligation under local anesthesia was performed by Dr. Orvar Swenson. A marked rise in temperature which later occurred subsided within twenty-four hours after the cessation of sulfadiazine therapy. The patient was discharged from the hospital on Oct. 4, 1944.

Since his discharge, he has been seen at frequent intervals. He never complains of anginal pains, either at rest, after meals, or after exercise. On Oct. 27, 1944, he developed a pleuropulmonary infection on the right side which subsided rapidly after treatment. Exercise tolerance tests were carried out on and following Dec. 5, 1944, by Dr. J. E. F. Riseman. After twenty-eight trips on the two-stair apparatus, he did not develop pain. The electrocardiograms taken after exercise were quite similar to the postexercise tracings taken before surgery. At that time the tracing showed only minimal S-T depression.

The patient has been seen recently and states that he is much improved, has no more pain, and has resumed his work.

SUMMARY

A case of coronary disease with angina has been reported. Pericoronary neurectomy combined with ligation of the great cardiac vein was carried out six months ago. Since the operation the patient has shown much improvement, has had no pain, and has been able to work.

REFERENCES

1. Leriche, R., and Heitz, J.: De la réaction vaso-dilatatrice consécutive à la résection d'un segment artériel oblitéré, Compt. rend Soc. de biol. **30**: 160, 1917.
2. Leriche, R.: Résultats éloignés des ligatures et des résections artérielles, Rapports XXXIe Congrès de l'Ass. Française de Chir., Oct., 1922.
3. Leriche, R.: A propos de l'embolectomie et de l'artériectomie dans les thromboses oblitérantes, Bull. et Mém. Soc. Nat. de Chir. **57**: 524, 1931.
4. Leriche, R., and Stricker, P.: L'artériectomie dans les artérites oblitérantes. Etude expérimentale et thérapeutique, Paris, 1933, Masson et Cie.
5. Leriche, R.: Considérations sur le traitement des artérites et des embolies artérielles, d'après une centaine de cas, Lyon méd. **151**: 393, 1933.
6. Leriche, R., and Fontaine, R.: Chirurgie des nerfs du coeur, Rapports XLIe Congrès de l'Ass. Française de Chir., Oct., 1932.
7. Oppel, W. A.: Wieting's Operation und der reduzierte Bluvkieislavg, Wratschebnaja Gazetta **40**: 1241, 1913.
8. Gross, L., Blum, L., and Silverman, G.: Experimental Attempts to Increase the Blood Supply to the Dog's Heart by Means of Coronary Sinus Occlusion, J. Exper. Med. **65**: 91, 1937.
9. Fauteux, M.: A New Method for Developing a Better Collateral Blood Supply to the Heart, Canad. M. A. J. **38**: 186, 1938.
10. Fauteux, M.: Experimental Study of the Surgical Treatment of Coronary Disease, Surg., Gynec. & Obst. **71**: 151, 1940.
11. Fauteux, M.: Positions actuelles du traitement chirurgical de l'angine de poitrine, Union méd. du Canada **69**: 829, 1940.
12. Fauteux, M., and Palmer, J. H.: Treatment of Angina Pectoris of Atheromatous Origin by Ligation of the Great Cardiac Vein, Canad. M. A. J. **45**: 295, 1941.
13. Fauteux, M.: Etudes expérimentales sur le traitement chirurgical des coronarites, Union méd. du Canada **72**: 1260, 1943.

PAROXYSMAL PULMONARY EDEMA CONSEQUENT TO STIMULATION OF CARDIOVASCULAR RECEPTORS

I. Effect of Intra-arterial and Intravenous Infusions

Aldo A. Luisada, M.D., and Stanley J. Sarnoff, M.D.
Boston, Mass.

THE pathogenesis[1] and treatment[2] of paroxysmal pulmonary edema were recently reviewed by one of us (A. A. L.), and it was pointed out that there are two conflicting theories as to the pathogenesis. The first explains the syndrome as the effect of sudden failure of the left ventricle with a normally functioning right ventricle.[3-6] The other theory attributes the edema to a sudden increase in the permeability of the lung capillaries caused by nerve reflexes.[7-9]

In previous attempts to produce acute pulmonary edema similar to that seen in hypertensive patients, the following experimental devices have been used: (a) massive injection of adrenalin (in rabbits)[10-14]; (b) ligature of the aortic arch and of some of its efferent arteries (in rabbits or dogs)[3, 15-17]; and (c) massive intravenous infusion of saline solution (in rabbits, cats, and dogs).

Slow infusion of saline into the veins of the dog can be continued for hours, until enormous amounts have been introduced, without producing any symptoms, as Wiggers[18] has shown. Therefore, various authors[19-21] have resorted to the device of cutting the vagi before the infusion in order to produce edema.

Rapid intravenous infusion of even an enormous quantity of fluid, amounting to three times the blood volume, given in less than thirty minutes, only irregularly produces edema of the lungs. It has been found, however, that the rapid *intracarotid* infusion of saline solution produces pulmonary edema more consistently.[24, 25]

The technique and preliminary results have been described elsewhere.[25]

METHODS

Mongrel dogs weighing 5 to 20 kg. were used. Smaller dogs and pregnant bitches were found to be unsuitable. Anesthesia was induced by the subcutaneous injection of 3 mg. of morphine sulfate per kilogram of body weight. This was followed twenty minutes later by 1 Gm. per kilogram of body weight of urethane given by stomach tube. Occasionally, a small additional amount of urethane was required. The choice of anesthesia is important, since sedatives and anesthetics may inhibit experimental pulmonary edema.[13, 17, 20, 26] In early experiments we used chloralose, but when this drug became unobtainable we resorted to the use of urethane, which we found almost as satisfactory since it has no action on cardiovascular receptors.[26, 27]

From the Surgical Research Laboratory of the Beth Israel Hospital, Boston, Massachusetts.
This paper was read before the New York Cardiological Society, Oct. 25, 1944.
Received for publication June 9, 1945.

Infusion.—Arterial infusions into the carotid and the femoral arteries were given with the cannulae directed toward the periphery (head, legs); venous infusions were given with the cannulae directed centrally. Large amounts of isotonic saline solution, Tyrode's solution, bovine albumin-salt solution, and blood were administered separately under high pressure. Arterial infusions were given under a pressure of 280 to 300 mm. Hg and venous infusions under a pressure of 50 to 150.

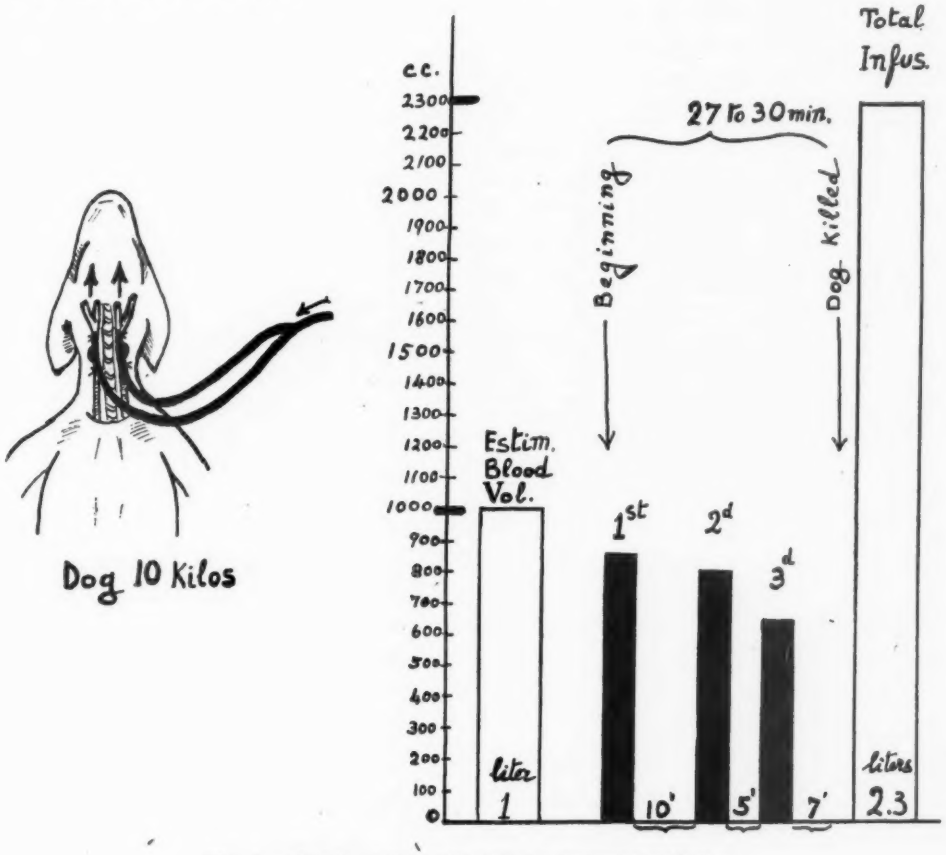


Fig. 1.—Sketch of the method for interrupted infusion.

In the first series of experiments uninterrupted infusion of fluid was continued until the death of the dog. In a second series it was thought preferable to alternate periods of infusion with periods of rest in order to avoid anoxemia of the brain, to permit the development of the edema, and to limit the total amount of fluid used.

The total quantity of injected fluid usually amounted to 2.3 times the animal's estimated blood volume. The blood volume was estimated to be 10 per cent of the animal's total weight. The total volume of infused fluid was occasionally varied for different purposes. The initial infusion was 85 per cent of the animal's estimated blood volume and was administered in from one to two

and one-half minutes depending on the size of the dog. Ten minutes after starting the first infusion another infusion amounting to 80 per cent of the original blood volume was given. Five minutes after the end of the second infusion 65 per cent of the original blood volume was infused and required a correspondingly shorter period of time. If the animal survived this procedure, it was sacrificed seven minutes after the end of the last infusion. The trachea was clamped, the inferior vena cava was cut, the heart was severed from its connections, and the lungs were removed within two to three minutes.

The fluid to be infused was contained in a large bottle. The pressure in the air chamber of the bottle was controlled by means of a pump and was measured with an aneroid manometer. The fluid escaped through a rubber tube and entered the two glass cannulae connected to the two common carotid arteries. The proximal ends of the vessels were tied at the beginning of the experiment and were left so until the end. Because of the ligation of the common carotids, the artificially high pressure present in the carotid arteries during the short periods of infusions was followed by longer periods of low carotid pressure.

Evaluation of the Edema.—In some of the first experiments we tried to detect pulmonary edema by physical examination. This proved to be unsatisfactory. All animals developed dyspnea during the experiment. This was nearly always accompanied by bronchospastic phenomena and either dry, whistling, or crackling noises were audible upon auscultation. Moist râles were difficult to recognize because of the other auscultatory findings. Pink froth coming out of the nose unmistakably indicated the existence of edema. However, the tremendous hypertension in the head may lead to salivation and occasionally bleeding from the gums and nose. This may result in confusing gurgling sounds which are not due to pulmonary edema. Vomiting sometimes occurs.

In other experiments we tried to detect the presence of edema by opening the trachea and observing the spontaneous outpouring of frothy sputum. This also proved deceptive; in some experiments moderate edema gave rise to early outpouring of frothy material; in others, severe edema did not. Therefore, we decided that only data based on post-mortem findings were to be relied upon in determining the presence and degree of pulmonary edema.

The gross appearance of the lungs and the presence of foam in the trachea were noted. The trachea was clamped and cut 2 inches above the carina, and the lungs were weighed without any loss of fluid from the trachea. The lungs were then inverted and squeezed firmly in order to note the character and amount of fluid and foam which they contained. Section of the parenchyma likewise yielded information as to the amount of edema present in different lobes.

The normal weight of the lungs of animals sacrificed during other experiments was studied in early spring and in midsummer. By dividing the weight of the lungs in grams by the weight of the dogs in kilograms, we obtained an index representing the relative weight of the normal lungs, including a normal amount of blood. This is referred to as the *lung/body index.*

In early spring, when the temperature was still low, this index was found to vary between 0.75 and 1.05 and averaged 0.86.* In summer, when the temperature was high, the index was from 1.13 to 1.66 and averaged 1.33. Therefore, an index of 0.8 to 1.2 in winter and early spring and an index of 1.3 to 1.5 in summer may be considered a normal index for dogs given large amounts of fluid.

Fluids Used.—Four different types of fluid were employed: (a) Tyrode's solution; (b) physiologic salt solution; (c) a 5 per cent bovine albumin solution in normal saline†; and (d) oxygenated dog blood. All fluids were injected at 37° C. When the injections were repeated at room temperature the results were the same. Fine, Seligman, and Frank[28] have demonstrated that dogs tolerate bovine albumin. Dog blood obtained by bleeding two heparinized dogs before the beginning of the experiment was kept for about an hour at 37° C. and shaken before use in order to saturate the red cells with oxygen.

Tracings and Evaluations.—Venous pressure was determined by the Kennedy-Lyon-Burwell technique. Arterial pressure was determined by direct femoral puncture or cannulation. Heparin was used in the latter instance. In some animals kymographic tracings were made. Electrocardiographic and phonocardiographic records, as well as roentgenograms of the chest, were obtained in several experiments. By considering gross observations together with the lung weights we graded the edema from 1 to 4. The procedure employed is indicated in Table I.

TABLE I. FINDINGS USED IN GRADING THE DEGREE OF PULMONARY EDEMA

INDEX LUNG/BODY	FOAM	EDEMA
1.20-1.60	None	- (congestion)
1.40-2	Slight	+
1.40-2	Abundant	++
1.60-2.75	Fair amount	++
1.60-2.75	Abundant	+++
2.75-5 (or above)	Abundant	++++

TABLE II. CONTINUOUS INFUSION INTO CAROTID ARTERIES

SERIAL NUMBER OF EXPERIMENT	WEIGHT OF THE DOGS (KG.)	AMOUNT OF FLUID AS COMPARED TO ESTIMATED NORMAL BLOOD VOLUME	INDEX LUNG/BODY	GRADE OF EDEMA	ANESTHESIA	MODE OF DEATH
8A	20	About 3	-	++	Chloralose	Spontaneous
9A	24	About 3	-	++++	Chloralose	Spontaneous
11A	19	1	-	+	Chloralose	Spontaneous
13A	27	3	-	+++	Chloralose	Spontaneous
17	7.4	2.5	3.37	++++	Urethane	Spontaneous
44	12.7	1.5	1.96	+	Urethane	Dog killed

*In a study on the weight of the lungs of normal dogs, Wood and Moe[31] obtained an index of 0.8, with a minimum of 0.54 and a maximum of 0.97. Since these dogs were killed by bleeding, the lungs had a subnormal content of blood and, therefore, a lower weight.

†This was provided by the Armour and Company, Chicago, Ill., through the courtesy of Prof. E. J. Cohn, Department of Physical Chemistry, Harvard Medical School.

RESULTS

Continuous Carotid Infusions.—Continuous infusion of saline was used in six experiments. The external and internal carotid arteries and some of the small branches were ligated in five of them, so that the fluid entered the animal only through the small vessels originating immediately above the carotid sinus. Death of the dogs occurred after amounts of fluid varying from one to three times the blood volume had been injected (Table II).

Standard Interrupted Carotid Infusion.—Infusions given in three interrupted periods sometimes caused the death of the animal. The first infusion generally produced slight dyspnea; the second was accompanied and followed by severe dyspnea; and the third was followed by extreme dyspnea, then apnea and death. Pink froth often poured from the nostrils between the second and third infusions or during the latter (Table III).

Infusion with *Tyrode's solution* produced far less severe dyspnea than infusion with saline: dyspnea was entirely absent in one experiment (Table IV). Infusion with *bovine albumin-salt solution* resulted in dyspnea comparable to

TABLE III. STANDARD INTERRUPTED INFUSION INTO THE CAROTID ARTERIES WITH PHYSIOLOGIC SALT SOLUTION

SERIAL NUMBER OF EXPERIMENT	WEIGHT OF THE DOGS (KG.)	AMOUNT OF FLUID AS COMPARED TO ESTIMATED NORMAL BLOOD VOLUME	INDEX LUNG/BODY	GRADE OF EDEMA	MODE OF DEATH	REMARKS
27	7.7	2.5	1.89	++	Dog killed	-
31	8.6	2.8	2.44	+++	Dog killed	-
46	9	2.5	4.44	++++	Dog killed	-
50	6.4	2.4	2.74	+++	Dog killed	Tracheotomy
58	10.4	2.3	2.75	+++	Dog killed	-
64	9.6	2.3	1.69	++	Dog killed	Ligature of jugular veins
80	13.4	2.5	1.86	+++	Dog killed	-
89	8	2.3	5.40	++++	Dog killed	Tracheotomy
92	13	2.3	2.69	+++	Spontaneous death	-
102	19	2.3	5.26	++++	Spontaneous death	-

TABLE IV. STANDARD INTERRUPTED INFUSION INTO THE CAROTID ARTERIES WITH DIFFERENT FLUIDS

SERIAL NUMBER OF EXPERIMENT	WEIGHT OF THE DOGS (KG.)	AMOUNT OF FLUID AS COMPARED TO ESTIMATED NORMAL BLOOD VOLUME	INDEX LUNG/BODY	GRADE OF EDEMA	MODE OF DEATH	FLUID
1	11.2	3	-	+++	Spontaneous	Tyrode's
56	8.2	2.3	1.56	+	Dog killed	Tyrode's
59	5.7	2.5	1.36	-	Dog killed	Tyrode's
60	5	2.5	2.56	++	Dog killed	Tyrode's
61	15.9	2.3	2.78	+++	Dog killed	Tyrode's
5	13.4	2	5.22	++++	Spontaneous	Bovine albumin-salt solution
34	9.8	1.9	2.29	+++	Spontaneous	Bovine albumin-salt solution
55	7.2	2.3	4.72	++++	Dog killed	Blood

that caused by saline solution. It also produced severe edema (Table IV). Infusion with *blood* caused only moderate dyspnea but very severe edema (Table IV).

Infusion made into only one carotid artery produced moderate pulmonary edema.

Infusion Into Other Vessels.—Infusion was made into the femoral arteries of five animals in a manner similar to that used for the standard infusion into the carotids, except that two and one-half to three times the estimated blood volume was introduced. Three out of five dogs had perfectly dry lungs, one had moderate pulmonary edema, and one had severe pulmonary edema (Table V).

TABLE V. STANDARD INFUSION INTO THE FEMORAL ARTERIES

SERIAL NUMBER OF EXPERIMENT	WEIGHT OF THE DOGS (KG.)	AMOUNT OF FLUID AS COMPARED TO ESTIMATED BLOOD VOLUME	INDEX LUNG/BODY	GRADE OF EDEMA	MODE OF DEATH	FLUID	REMARKS
2	12.2	2.9	0.9	-	Dog killed	Tyrode's	--
78	5.3	3	1.26	-	Dog killed	Saline	
81	11.4	3	2.45	+++	Dog killed	Saline	Summer
84	5.2	2.5	1.58	+	Dog killed	Saline	Summer
90	7.8	2.5	1.18	-	Dog killed	Saline	--
38	12.5	2.4	1.64	+	Dog killed	Saline	Infusion toward the center

Infusions into veins were made under pressure of from 50 to 150 mm. of mercury. In one experiment the jugular veins were used, with the fluid injected toward the heart. In all others the femoral veins were used, with the fluid also directed toward the heart. Severe pulmonary edema occurred in only two out of eight dogs, while minimal edema developed in one (Table VI).

TABLE VI. STANDARD INFUSION INTO VEINS

SERIAL NUMBER OF EXPERIMENT	WEIGHT OF THE DOGS (KG.)	AMOUNT OF FLUID AS COMPARED TO ESTIMATED BLOOD VOLUME	INDEX LUNG/BODY	GRADE OF EDEMA	MODE OF DEATH	PRESSURE (MM. HG)	REMARKS
3	14	2.7	-	-	Dog killed	50	Absolutely dry lungs. 1 femoral vein
11	17	1.7	1.05	-	Dog killed	100-120	1 femoral vein
51	10	3	1.25	-	Dog killed	110-120	Jugular veins
65	10	3	4.05	+++	Dog killed	140-160	Femoral veins
67	9.3	2.3	1.35	-	Dog killed	110-120	Femoral veins
68	10.9	3	1.46	+	Dog killed	120	Femoral veins
83	7.8	2.3	1.31	-	Dog killed	100	Femoral veins
91	10.9	2.3	3.94	++++	Dog killed	100	Femoral veins —summer

Effect of Infusion Upon Arterial and Venous Pressure.—Femoral arterial pressure was measured in two standard experiments and recorded graphically in a third. After occlusion of the common carotid arteries the blood pressure rose to 170 to 190, but returned to normal levels during the first infusion. The same alternation of high and normal blood pressure was repeated during the second infu-

sion, but there was a gradual tendency for the blood pressure to rise. After the end of the third infusion the systolic pressure was higher than at any previous time, though not markedly so; it reached 170 mm. Hg in two experiments and 160 mm. Hg in another.

Femoral venous pressure was measured in four experiments. From a normal figure of 3 to 7 cm. of water the pressure rose to 50 to 70 at the end of the first infusion, but returned to normal within five to eight minutes. It rose to 75 to 85 at the end of the second infusion and fell to 20 to 35 at the end of the rest period. It reached 95 to 100 at the end of the third infusion, and dropped later to 15 to 30 just before the animals were sacrificed.

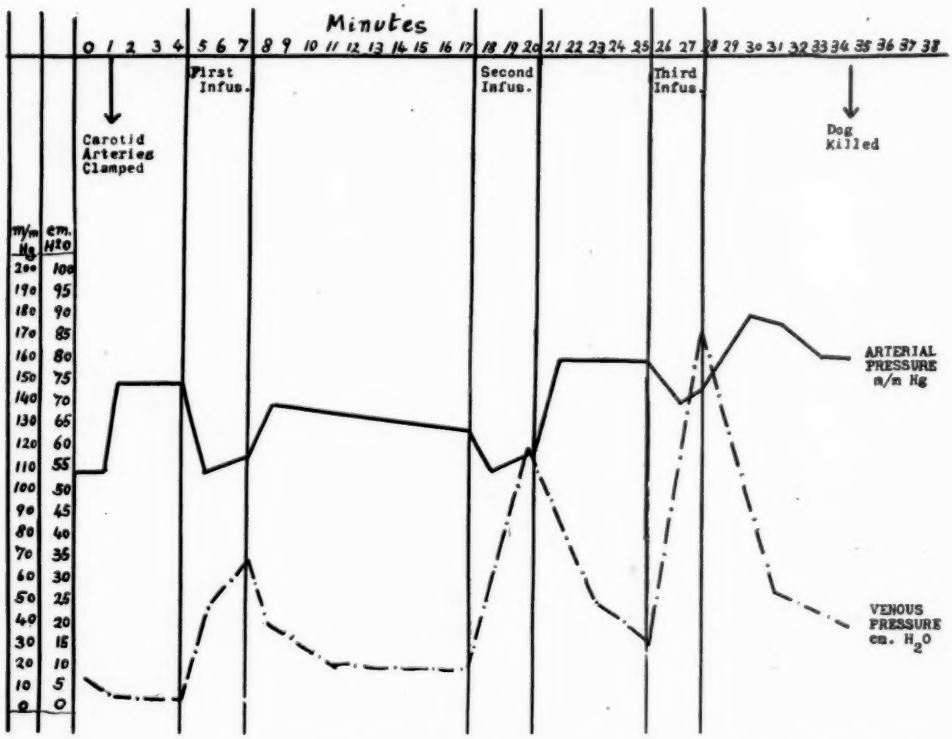

Minutes
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38
First Infus.
Second Infus.
Third Infus.
Carotid Arteries Clamped
Dog Killed
m/m Hg
cm. H2O
ARTERIAL PRESSURE m/m Hg
VENOUS PRESSURE cm. H2O

Fig. 2.—Changes of the venous and arterial pressures during the standard infusion of one dog.

Electro- and Phonocardiograms.—These graphic studies were recorded in two experiments. Cannulation accelerated the heart rate from an average of 115 per minute to an average of 140. The heart rate reached 180 after the first infusion but rose no higher after subsequent infusions. Sinus rhythm was maintained. All waves in the electrocardiogram became smaller, and either inversion or flattening of the T waves developed.

The phonocardiogram showed signs of myocardial strain, such as gallop rhythm or diastolic rumble, and a terminal decreased amplitude of the second sound. A functional systolic murmur was observed in one experiment.

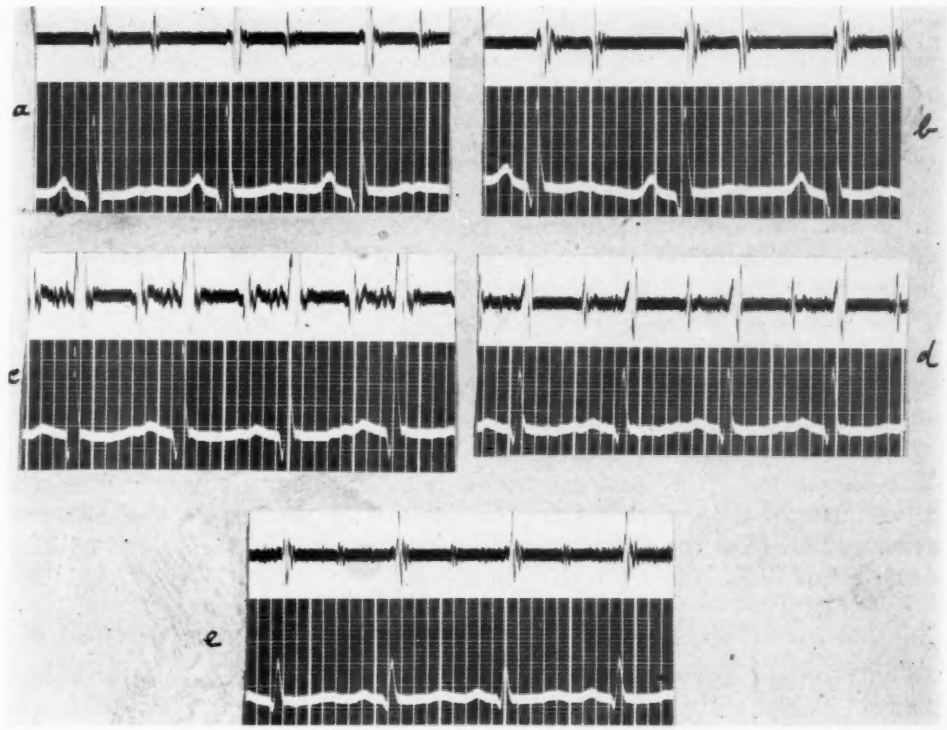
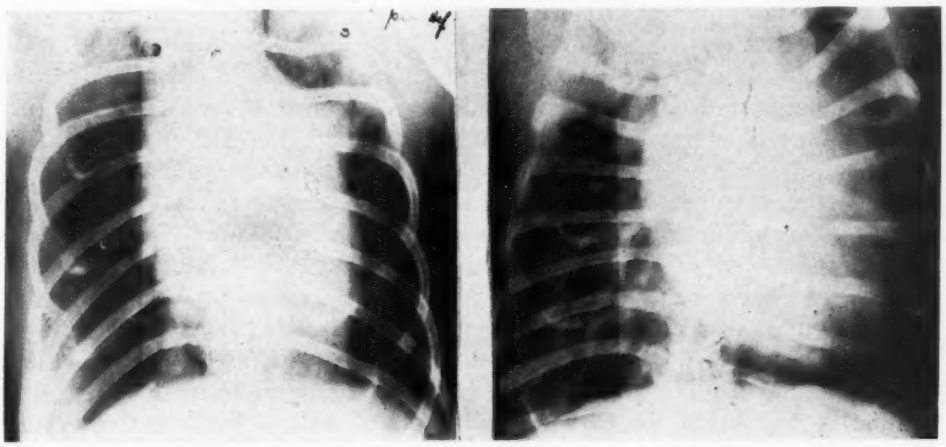


Fig. 3.—Electro- and phonocardiogram of a dog during the standard infusion: *A*, before cannulation of the carotids; *B*, after cannulation; *C*, after the first infusion; *D*, after the second infusion; and *E*, after the third infusion, immediately before death.



A. *B.*

Fig. 4.—X-ray of the thorax of a dog: *A*, before any infusion; and *B*, after the third infusion. Remarkable enlargement of the heart and of the chest. Haziness of the lung fields.

Roentgenograms.—Films of the thorax were taken in three experiments with the animal lying flat on the back. The condition of the heart and lungs was studied and compared before cannulation, after the second infusion, and after the third. The tremendous increase in the blood volume and the storage of fluid in the blood reservoirs made the comparison difficult because the thorax was apparently increased in size. This was the result (a) of increased size of the heart; (b) of increased size of the abdominal organs; and (c) of vascular distention, edema, and compensatory emphysema of the lungs. All these factors caused widening of the intercostal spaces. The edema was indicated by the haziness of the lung fields.

Post-Mortem Findings.—Fluid was present in the abdominal cavity. The urinary bladder was distended and the small bowel contained fluid. However, very little or no fluid was present in the pleural and pericardial cavities. Both the liver and the spleen were distended and cyanotic. Cyanosis of the abdominal organs was remarkable. The stomach was tremendously distended both by fluid and by gas. The heart was uniformly enlarged but not flabby. The lungs were distended and showed red patches separated by pale areas. Whitish or pink foam poured from the cut trachea, and from the parenchyma a red bubbling froth flowed which was increased by squeezing.

DISCUSSION

This study was made in order to re-evaluate earlier experiments[24] bearing on the possibility of producing pulmonary edema by the perfusion of the isolated head. We were able to demonstrate that in those earlier experiments fluid escaped from the head into the trunk through venous channels. This led to the present systematic study of (a) infusion into various vessels, (b) infusion into the carotid arteries with unimpaired venous return to the heart, and (c) infusion into the carotid arteries by means of a new technique.

Paroxysmal pulmonary edema, caused by the rapid infusion of fluid under high pressure into the carotid arteries, is only one aspect of a complex picture of transudation into serous cavities and into the lumen of various organs, such as the bronchial tree and the gastrointestinal tract. However, there is no definite connection between the amount, or even the existence, of pulmonary edema and the degree of transudation elsewhere. As a matter of fact, experiments with rapid infusion into veins often caused a remarkable degree of ascites without the production of any pulmonary edema. Moreover, the pulmonary edema produced by carotid infusion may be prevented by various procedures to be described, without changing the volume of the ascites, of the transudation into the gastrointestinal tract, or of the salivation. This shows that pulmonary edema is a particular aspect of the picture, and that the rapid increase of the blood volume is only one of the factors leading to transudation into the alveoli. Experiments with infusion into other vessels confirm this conclusion. If we exclude the experiment of infusion into the femoral arteries toward the heart, which may be explained in a different way, we obtain the following results: (a) In thirteen experiments with infusion either into veins or into femoral ar-

teries, where the average amount of infused fluid was 2.57 times the blood volume, pulmonary edema was found in 27.7 per cent of the dogs. (b) In eighteen experiments with infusion into the carotid arteries, where the average amount of infused fluid was 2.38 times the blood volume, pulmonary edema was found in 89 per cent of the dogs. This shows that *the amount of fluid plays only a secondary role* and that *the route of infusion is of primary importance.*

Viscosity of the fluid seems to act in an inverse way; the more viscid the fluid the greater the edema. Obviously, when the infused fluid has a low viscosity it is excreted, secreted, and stored with such speed that the venous return to the heart is relatively less than when it has a high viscosity. This factor is more important than ability of the fluid to penetrate the walls of the lung capillaries, and accounts for lower grades of pulmonary edema with Tyrode's solution and saline than with albumin or blood. This conclusion is in agreement with that of Yeomans, Porter, and Swank.[23]

The chemical composition of the fluid is of some importance. When either Tyrode's solution or blood is substituted for plain saline, the dyspnea is very much less severe. This can be attributed to the presence of calcium and potassium ions, and in the latter case to the presence of oxygen. The absence of these substances is likely to effect the receptors of the carotid body and the brain centers. The effect on the lung capillaries is considerably less, since the fluid is mixed with blood before reaching them. However, in spite of this fact, pulmonary edema may occur with either Tyrode's solution or blood.

Asphyxia is not likely to occur because of the shortness of the periods of infusion. Moreover, infusion with oxygenated blood was followed by pulmonary edema, which excludes the possibility of this mechanism.

The systemic blood pressure rises after occlusion of the common carotid arteries, falls during the infusion (carotid sinus reflex), and then rises again. The maximum level, found toward the end, when the effect of occlusion of the carotid arteries was added to that of increased blood volume, was about 170 mm. of mercury. Therefore no permanent arterial hypertension plays any part in these experiments.

Venous hypertension undoubtedly occurs; extreme figures may be reached for a short time. This may be an important element in the causation of the edema. However, venous infusion under pressure far higher than that obtained by standard carotid infusion, caused pulmonary edema in only a small percentage of the experiments.

Distention of the heart should be considered. The dog's heart dilates tremendously during the infusion, but this distention should not be considered as a manifestation of failure. This is borne out by the slight changes in the electrocardiogram, the preservation of normal rhythm, the moderate auscultatory signs of strain, and by the fact that upon section the heart is often found beating strongly and may even continue to do so after excision. In spite of these facts, distention of the heart may play a part and will be studied later.

The pulmonary edema which is brought about in dogs by the use of interrupted carotid infusion cannot be explained without taking into account factors

which are not purely mechanical. Vascular changes, nervous reflexes, and humoral mechanisms are being investigated and will be reported subsequently.

The evaluation of pulmonary edema produced by our technique must take into account seasonal conditions. We have observed that when experiments were made in the summer, the dogs had poor resistance and died early, often with a more severe pulmonary edema than was produced in other seasons. This can be explained by the fact that dogs have very few sweat glands and depend chiefly upon panting and vaporization of water for keeping their body temperature within reasonable limits.[29] This mechanism, which may produce overventilation of the alveoli and may change the chemical composition of the blood[30], both stimulates the medullary centers and causes a greater amount of blood to pass through the lungs in a given unit of time. That the latter occurs is demonstrated by the high lung/body index which we found in summer in comparison with that found in early spring. The hyperemia of the lungs, the greater stimulation of the respiratory center, and the frequent alkalosis are all factors that must be taken into consideration.

SUMMARY

1. A new experimental procedure for producing acute pulmonary edema in dogs is described. The basis of the method is the rapid infusion of massive quantities of fluid into the common carotid arteries, toward the head. The infusion is performed in three short, interrupted periods within a half hour, under a pressure of 280 to 300 mm. Hg. The quantity of fluid introduced amounts to 2.3 times the dog's estimated blood volume. This procedure produced pulmonary edema in nearly all experiments.

Clinical manifestations and electrocardiographic, roentgen, and post-mortem findings are discussed.

2. The effect of infusion of either the same amount or a larger amount of fluid into the femoral arteries and into veins has been studied and compared with the results of intracarotid infusion. Pulmonary edema is produced by these methods in only a few experiments.

3. The effect of varying the chemical composition of the fluid is discussed.

4. Neither the amount of fluid injected nor the rate of its injection determines the production of edema. Factors other than mechanical ones are involved in the production of the form of pulmonary edema which is being investigated.

REFERENCES

1. Luisada, A.: The Pathogenesis of Paroxysmal Pulmonary Edema, Medicine **19**: 475, 1940.
2. Luisada, A.: The Treatment of Paroxysmal Pulmonary Edema, Exper. Med. & Surg. **1**: 22, 1943.
3. Welch, W. H.: Zur Pathologie des Lungenoedems, Virchows Arch. f. path. Anat. **72**: 375, 1878.
4. Fraentzel, O.: Die Krankheiten des Herzens, Berlin, 1889.
5. Lian, C.: Le Sindrome D'Insuffisance Ventriculaire Gauche, Presse méd. **18**: 49, 1910.
6. Vaquez, H.: Les Grands Sindromes d'Insuffisance Cardiaque, Eighth Int. Meeting Med. Sci. (5th Section), London, 1913.
7. Teissier, J.: Comptes Rendus, XIII Congrès Internat. de Méd., Paris, 1900, Masson & Cie.

8. Wassermann, S.: Das akute kardiale Lungenoedem und sein reflektorische Mechanismus, Wien. Arch. f. inn. Med. **24**: 213, 1933; **24**: 387, 1934.
9. Luisada, A.: I Fattori Nervosi dell' Edema Polmonare Acuto. Atti XXXVI Congr. Soc. Ital. Med. Int., Roma, 1931, Luigi Pozzi.
10. Meltzer, S. J.: Edema: A Consideration of the Physiologic and Pathologic Factors Considered in Its Formation, Am. Med. **8**: 191, 1904.
11. Josué, O., and Bloch, L.: Oedeme Aigü du Poumon Expérimental, etc. Bull. et mém. Soc. méd. d. hôp. de Paris **25**: 55, 1908.
12. Auer, J., and Gates, F. L.: Experiments on the Causation and Amelioration of Adrenalin Pulmonary Edema, J. Exper. Med. **26**: 201, 1917.
13. Luisada, A.: Beitrag zur Pathogenese und Therapie des Lungenoedems, Arch. f. exper. Path. u. Pharmakol. **132**: 313, 1928.
14. Boggian, B.: Il Valore degli Interventi Operatori sul Simpatico Cervico-Toracico, Minerva med. **9**: 967, 1929.
15. Sahli, H.: Zur Pathologie des Lungenoedems, Arch. f. exper. Path. u. Pharmakol. **19**: 433, 1889.
16. Kotowschtschikow, A. M.: Zur Frage nach den Veraenderungen der Herztaetigkeit und des Blutkreislaufes bei acutem Lungenoedem, Ztschr. exper. Path. **13**: 400, 1913.
17. Antoniazzi, E.: Ricerche Sperimentali sui Fattori Meccanici e Nervosi dell' Edema Polmonare "Meccanico," Arch. per le sc. med. **54**: 818, 1930.
18. Wiggers, C. J.: Physiology in Health and Disease, Philadelphia, 1939, Lea & Febiger, p. 695.
19. Kraus, F.: Ueber Lungenoedem, Ztschr. exper. Path. **14**: 402, 1913.
20. Brunn, F.: Ueber Lungenoedem, Med. Klin. **30**: 483 and 520, 1934.
21. Farber, S.: Neuropathic Pulmonary Edema: Further Observations, Arch. Path. **30**: 180, 1940.
22. Cutting, R. A., Larson, P. S., and Lands, A. M.: Cause of Death Resulting From Massive Infusions of Isotonic Solutions, Arch. Surg. **38**: 599, 1939.
23. Yeomans, A., Porter, R. R., and Swank, R. L.: Observations on Certain Manifestations of Circulatory Congestion Produced in Dogs by Rapid Infusion, J. Clin. Investigation **22**: 33, 1943.
24. Luisada, A.: Ipertensione Encefalica e Edema Polmonare Sperimentale di Natura Riflessa-Atti Soc. Medico.-Chir. di Padova, May 2, 1930.
25. Luisada, A., and Sarnoff, S. J.: Studies on Paroxysmal Pulmonary Edema: A New Experimental Method, Proc. Soc. Exper. Biol. & Med. **57**: 279, 1944.
26. Jarisch, A., Richter, H., and Thoma, H.: Zentrogenes Lungenoedem, Klin. Wchnschr. **18**: 1440, 1939.
27. Heymans, C., Bouckaert, J. J., and Regniers, P.: Le Sinus Carotidiens et la Zone Homologue Cardio-Aortique, Paris, 1933, Gaston Doin & Cie.
28. Fine, J., Seligman, A. M., and Frank, H. A.: Studies on Traumatic Shock, J. Clin. Investigation **23**: 731, 1944.
29. Dill, D. B.: Life, Heat and Altitude, Cambridge, 1938, Harvard University Press.
30. Rice, H. A., and Steinhaus, A. H.: Acid-Base Changes in the Serum of Exercised Dogs, Am. J. Physiol. **96**: 529, 1931.
31. Wood, E. H., and Moe, G. K.: The Measurement of Edema in the Heart-Lung Preparation, Am. J. Physiol. **136**: 506, 1942.

PAROXYSMAL PULMONARY EDEMA CONSEQUENT TO STIMULATION OF CARDIOVASCULAR RECEPTORS

II. Mechanical and Neurogenic Elements

Aldo A. Luisada, M.D., and Stanley J. Sarnoff, M.D.
Boston, Mass.

A NEW method of producing acute pulmonary edema in dogs based upon rapid intracarotid infusion of massive quantities of fluid toward the head was described in a previous article.[1] Fluid amounting to more than twice the dog's estimated blood volume was infused into the carotid arteries under a pressure of 280 to 300 mm. Hg, in three short interrupted periods, which occupied half an hour in all. The study has been continued in an attempt to evaluate the role of the various mechanical and neurogenic elements in the production of this type of experimental pulmonary edema.

A. MECHANICAL FACTORS

Methods.—The influence of *gravity* was studied by keeping the animal either lying on one side or in the standing position throughout the period of infusion. The influence of dynamic changes secondary to spasm of the glottis was studied by performing a *tracheotomy* either prior to the first infusion or immediately after it. The effects of varying pressure conditions in the respiratory tree were studied by using the following procedures: (a) tracheotomy followed by artificial respiration with an interrupted positive pressure of 8 cm. of water; (b) tracheotomy followed by artificial respiration with an interrupted negative pressure (suction) of 8 cm. of water; and (c) tracheotomy and continuous insufflation of air under a lateral pressure of 10 cm. of water near the carina through a Foley catheter.

The effect of *bleeding* was studied in the following way. Following heparinization, the standard intracarotid infusions were performed. During the second and third infusions, however, amounts of blood equal to the volume of infusion were taken from the femoral artery. The blood obtained during the second infusion was used as the infusion fluid for the third infusion.

Results.—The effect of *gravity* fully explains the congestion which is constantly present in the posterior part of the lungs when the dogs are perfused by means of the standard technique. Dogs kept lying on one side show an intense congestion of the lung on the dependent side which is revealed by the cyanotic color of its surface. However, this congestion does not vary with the edema, as the lung of the upper side is lighter in color, but may be heavier in weight than the other. Dogs kept standing during the experiment show the same intensity of pulmonary edema as the others but exhibit very marked congestion of the lower lobes, both in the back and in the front.

The effect of rapid *bloodletting* during the infusion was demonstrated in a striking way by the fact that the dogs so treated did not show any trace of pul-

From the Surgical Research Laboratory of the Beth Israel Hospital, Boston, Massachusetts.
This paper was read before the New England Heart Association, Jan. 29, 1945.
Received for publication June 9, 1945.

TABLE I. THE EFFECTS OF VARIOUS PROCEDURES WHICH INFLUENCE RESPIRATION

SERIAL NUMBER OF EXPERIMENT	WEIGHT OF DOGS (KG.)	INTERVENTION	INDEX LUNG/BODY	GRADE OF EDEMA	REMARKS
50	6.4	Tracheotomy	2.74	+++	
89	8		5.4	++++	Summer
97	13		3.46	++++	Summer, premature death
32	10.4	Respiration by suction	3.29	++++	
28	10	Respiration by pressure	1.18	-	
37	6	Respiration by pressure	1.28	-	
41	7	Respiration by pressure	1.07	-	
96	11	Respiration by pressure	1.75	+	Summer. Artificial respiration started after first infusion
73	8.2	Continuous air insuflation	1.19	-	
66	8.4	Expiratory valve	1.92	+	Valve in use all of the time
72	12.7	Expiratory valve	1.48	+	Valve applied at the end of first infusion
98	13	Expiratory valve	1.42	+	Valve in use all of the time. Very hot day. Incomplete infusion due to premature death

monary edema, the *lung/body index* ranging from 0.8 to 1.21, as it does in normal dogs.[1]

The result of various procedures affecting respiration is shown in Table I.

Tracheotomy does not prevent pulmonary edema. *Artificial respiration by intermittent suction* intensifies the edema. On the contrary, *artificial respiration by either continuous or rhythmic insufflation of air under positive pressure* inhibits the formation of pulmonary edema. The same is true but to a lesser degree, when the resistance against which expiration must take place is increased.

B. NEUROGENIC FACTORS

Methods.—The importance of stimulation of the pressoreceptors of the carotid sinus was investigated (a) by mechanically distending the sinus regions without infusion, and (b) by denervating the carotid sinuses prior to infusion. In addition, some studies were made on the role of the vagus nerve and the sympathetic nervous system.

Mechanical Distention of the Sinus: This experiment was performed in large dogs under morphine (3 mg. per kilogram of body weight) and chloralose (0.1 Gm. per kilogram of body weight) anesthesia by means of a special device composed of a thin ureteral catheter at the end of which a small piece of latex rubber was fixed by means of ligatures. The catheter was connected to a manometer, to a pump with a valve, and to a Marey tambour, and was introduced into the cephalic end of the carotid artery to a point judged to be near the sinus area. The rubber bulb was then distended. If no change in the femoral pressure occurred, the air was allowed to escape through the valve and the sound was pushed 1 to 2 mm. further. After a few attempts a point was found where the distention caused a sudden and marked hypotension, coupled

with bradycardia and respiratory changes. By the use of two ureteral catheters it is possible to stimulate both carotid sinuses at the same time.

Carotid Denervation: If a short interval or none at all was to be allowed before the beginning of the experiment on carotid denervation, morphine-urethane anesthesia was used, as described in the original technique,[1] and asepsis was dispensed with. If an interval of several days was to intervene between the denervation and the experiment, nembutal anesthesia was used and strict asepsis was adhered to. A ligature placed loosely around the common carotid artery provided sufficient traction to bring the bifurcation into view. A delicate mouse-toothed forceps was then used to remove the adventitia and nerve filaments from the entire carotid sinus area. In some experiments painting the sinus area with saturated phenol solution was also carried out. In one dog, infiltration with novocaine was used instead of denervation. Further experiments were made after cutting the vagi and after sympathectomy.

Vagus Section: This procedure was performed in the cervical region. The vagus nerve in dogs contains the depressor nerves and also the sympathetic trunk between the first cervical and stellate ganglion. Owing to the high position of the first cervical ganglion it is very difficult to isolate the real vagal fibers. For this reason the section was made rather low and just before the beginning of the infusion. In one experiment, infiltration of the vagi with 1 per cent procaine was substituted for vagus section.

Sympathectomy: Nembutal anesthesia was used and strict asepsis was adhered to in every case. Intermittent intratracheal insufflation accomplished pulmonary ventilation while the animal's chest was open. A 4-inch muscle-cutting incision along the third intercostal space was made. Gentle traction was made on the stellate ganglion and all rami from it were severed. The posterior parietal pleura was then carefully incised and the second, third, and fourth thoracic sympathetic ganglia were separated from their respective rami communicantes. The chain was removed intact. Hemostasis was secured and the ribs were approximated with heavy silk sutures.

Combined Vagal Stimulation and Intracarotid Infusion: In another type of experiment both intact vagi or the central or the peripheral ends of these nerves, were stimulated by means of a Harvard inductorium. This stimulation was alternated with intravenous infusion of a relatively moderate amount of fluid (from 1.2 to 1.8 times the blood volume) administered in three interrupted periods.

TABLE II. DISTENTION OF CAROTID SINUS BY RUBBER BALLOONS

SERIAL NUMBER OF EXPERIMENT	WEIGHT OF THE DOG (KG.)	INTERVENTION	CONGESTION	EDEMA
14A	23	One sinus	+	-
15A	21	One sinus	++	+
16A	28.5	Both sinuses	++	+
17A	34.5	Both sinuses	++	+
18A	36.8	Both sinuses	+	-
26A	18	Both sinuses	+	+
28A	22	One sinus plus slow venous infusion	+	+

Results.—The effects of mechanical distention of the carotid sinus are shown in Table II. A more or less pronounced congestion of the lungs was usually obtained, but no real edema. In some experiments, traces of edema were present in one lobe, but this was not comparable to the edema produced by our newer method[1] of infusion.

Results of denervation of the carotid sinus are shown in Table III. Pulmonary edema was produced in only two dogs out of seven.

TABLE III. RESULT OF STANDARD CAROTID INFUSION IN DOGS WITH PREVIOUSLY DENERVATED CAROTID SINUS

SERIAL NUMBER OF EXPERIMENT	WEIGHT OF THE DOGS (KG.)	INTERVENTION	INTERVAL	INDEX LUNG/BODY	EDEMA	REMARKS
40	16.4	Unilateral	1 hr. 40 min.	2.86	+++	
8	19	Bilateral		1.21	-	Spring
16	27	Bilateral	2 hr. 45 min.	1.09	-	Spring. Incomplete infusion due to premature death
30	23.4	Bilateral	4 days	1.06	-	Spring
33	10.4	Bilateral	Immediate	1.28	-	Spring. Procaine block
114	11	Bilateral	1 hr.	1.21	-	Fall
82	8.2	Bilateral	4 days	1.95	+	Summer
100	20	Bilateral	Immediate	1.95	+	Summer

Cutting the vagus nerves or infiltrating them with procaine had no apparent influence. Dogs so treated apparently died in the same way as the controls, and showed typical pulmonary edema with a high lung/body index. Cutting of the vagus nerves prior to venous infusion did not seem to increase the development of pulmonary edema.

TABLE IV. RESULTS OF SYMPATHECTOMY

SERIAL NUMBER OF EXPERIMENT	WEIGHT OF THE DOGS (KG.)	AMOUNT OF INFUSED FLUID	SIDE OF OPERATION	LUNG/BODY INDEX	EDEMA	SIDE ON WHICH THE LUNG IS HEAVIER
23	12	2.3	Right	2.20	+	Left
35	10.4	3.5	Right	2.69	++	Right
45	13.6	2.6	Right	1.17	-	Right
74	10.7	2.3	Bilateral	3	+++	-

After unilateral sympathectomy there appeared to be a greater resistance to the infusion and a tolerance of greater amounts of fluid (Table IV). On the other hand, unilateral lung changes were indefinite. In some experiments the weight of the lung on the operated side was greater, while in others, the lung on the intact side weighed more. Atelectasis, adhesive pleuritis, or slight unilateral pneumothorax on the operated side may have caused these variations. Moreover, the distribution of sympathetic fibers to the lungs is contralateral as well as ipsilateral.

Stimulation of either the central or the peripheral end of one vagus, the other vagus being intact, did not produce pulmonary edema, even when the venous infusion amounted to 1.8 times the estimated blood volume. Stimulation

of the two intact vagi during venous infusion of 1.8 times the blood volume was followed by severe pulmonary edema. Stimulation of the peripheral end of the cut vagi during a similar infusion caused severe pulmonary edema. Stimulation of the peripheral end of the cut vagi without venous infusion, done as a control, resulted in only slight congestion of the lungs. Stimulation of the central end of the cut vagi during venous infusion caused no pulmonary edema (Table V).

TABLE V. STIMULATION OF THE VAGI

SERIAL NUMBER OF EXPERIMENT	WEIGHT OF THE DOGS (KG.)	SURGICAL PROCEDURE	AMOUNT OF INJECTED FLUID AND RATE OF INJECTION	PRESSURE OF INJECTION (MM. HG)	INTERVENTION	INDEX LUNG/BODY	EDEMA
15	9	Procaine block of vagi	2.3 Carotid artery toward brain	260		1.8	++
99	10.5	Vagi cut	2.3 Carotid artery toward brain	260		2.9	+++
7	16		1.8 Femoral vein toward heart	100-120	Electric stimulation intact vagi	2.87	+++
110	15		1.8 Jugular vein toward heart	100-120	Electric stimulation intact vagi	2	+++
103	26	Right vagus cut	1.3 Jugular vein toward heart	100-120	Electric stimulation cephalic end left vagus	0.9	-
111	7.5	Vagi cut	1.8 Jugular vein toward heart	100-120	Electric stimulation cephalic end both vagi	1.05	-
106	19	Right vagus cut	1.3 Jugular vein toward heart	100-120	Electric stimulation cardiac end left vagus	1.11	-
112	9.5	Vagi cut	1.8 Jugular vein toward heart	100-120	Electric stimulation cardiac end both vagi	3.65	++++
115	9	Vagi cut			Electric stimulation cardiac end both vagi	0.83	-

DISCUSSION

We had previously demonstrated[1] that the rapid intracarotid infusion of fluid consistently causes pulmonary edema. The part played by the fluid itself when the standard technique was used was recognized as important but not as predominant. It was necessary, therefore, to investigate the part played by the sensitive receptors of the cardiovascular apparatus. Since one of the main results of the infusion is the distention of the carotid sinus, it is apparent that the receptors of this area are very important.

Prolonged mechanical distention of the sinus regions by means of rubber balloons caused severe respiratory and circulatory embarrassment, and occasionally death. As a result, the lungs showed severe congestion, but only occasional and slight edema. This can be attributed to the action of antagonistic mechanisms. On the one hand, a reflex arising in the carotid sinus affects the pulmonary vessels by a mechanism which will be discussed later; on the other

hand, this reflex causes a tremendous drop in systemic pressure and a decreased venous return to the heart, with the result that a relative ischemia of the lungs takes place.

The mechanisms by which a carotid sinus reflex might cause changes in the pulmonary vessels without greatly lowering the venous return are two: (1) distention of the carotid sinus plus artificially increased venous return to the heart (both factors are active in our standard method[1]); and (2) distention of the carotid sinus plus the action of a chemical substance maintaining a high pressure in the pulmonary circulation. The latter mechanism will be considered in a subsequent paper.

As for the first mechanism, if our assumption is correct, the two main factors must both be present: neither carotid sinus stimulation alone nor increased venous return alone will cause pulmonary edema. This has been shown to be true. Infusion of fluid alone did not consistently cause pulmonary edema when given by the standard technique: (a) into vessels other than the carotid arteries; (b) into only one carotid artery; (c) into denervated carotid arteries. On the other hand, distention of the carotid sinus did not cause pulmonary edema when: (a) there was no infusion, (b) when increase of venous return was prevented by simultaneous arterial bleeding.

In a few experiments moderate pulmonary edema was produced even when the infusion was made either into veins or into denervated carotid arteries. This occurred mainly during the summer. In the first paper of this series it was pointed out that in summer dogs have a certain degree of dilatation of the pulmonary vessels which is probably connected with the mechanism of panting. However, this dilatation does not completely explain the results mentioned. We believe that these results can be explained only by admitting that, even if carotid sinus reflexes have a paramount importance, other reflexes also play a part in producing the edema. Sensitive receptors are present in the aortic arch,[2, 11] the venae cavae,[3-5] the right auricle,[6, 7] the pulmonary veins,[5, 7, 9] the pulmonary artery,[8-13] the auricles,[5, 6] and the ventricles.[7, 11, 14, 15] All these receptors are stimulated by the rapid increase in the volume of circulating fluid which takes place in our experiments. However, the aortic receptors are stimulated only moderately, since the systemic blood pressure rises only moderately. The receptors of the venae cavae are highly stimulated, but for only a short time. On the other hand, stimulation of the receptors of the pulmonary artery is likely to cause a reflex dilatation not only of the peripheral vessels but also of the pulmonary vessels.[9, 10]

The severe and lasting distention of the heart itself also tends to produce a lasting stimulation of the ventricular and auricular receptors. The importance of these receptors has been emphasized in different types of experiments on pulmonary edema,[14-16] and also by the studies of Hochrein[17] which confirmed the existence of a cardiopulmonary reflex which brings about a dilatation of the pulmonary vessels.

Therefore we believe that the following factors should be considered in studying the pathogenesis of pulmonary edema: (a) mechanical distention

of the lung vessels due to fluid injected into the circulation; (b) changes of the lung vessels due to reflexes arising in the carotid sinus; and (c) changes of the lung vessels due to reflexes arising in the other parts of the cardiovascular apparatus, mainly in the heart itself.*

We believe that the role played by seasonal and temperature changes is due only in part to congestion of the lungs which is already present. The other and more important factor is a higher excitability of the nerve centers. This will favor the development of pulmonary edema by causing more intensive reflexes when all the cardiovascular receptors are stimulated and will more readily produce cardiopulmonary reflexes after denervation of the carotid sinus.

Mechanical distention due to fluid alone might undoubtedly be pushed to a point where pulmonary edema would occur with great frequency, whatever the route of injection. However, even were the amount of injected fluid tremendously increased, a large percentage of the dogs would die from acute heart failure without pulmonary edema, as our experiments have shown. It must be concluded, therefore, that the amount of fluid required for intracarotid infusion by our standard method is insufficient of itself to produce pulmonary edema; and that either vasomotor or permeability changes of the lung vessels are necessary factors for the production of the edema.

Our assumption is based partly upon the result of experiments made with denervation of the carotid sinus, partly upon those made by injection into veins, and partly upon pharmacologic experiments, which will be reported in a subsequent paper. Surgical intervention on the carotid sinus is easy. On the other hand, operation on other receptors is impractical.† This is why, after ascertaining the importance of the afferent pathway from carotid sinus to central nervous system, we tried the section of nerve fibers only in the efferent part of the reflex arc.

It is known that the carotid sinus reflex is based upon two different arcs: (a) a carotido-cardiac reflex with the efferent pathway by way of the vagus nerves,[18] which retards the cardiac action; and (b) a carotido-vascular reflex with the efferent pathway through the sympathetic system[19-20] which dilates the peripheral vessels.

In spite of the fact that knowledge about the vasomotor innervation of the pulmonary vessels[21] is still incomplete, it has been shown that a carotido-pulmonary reflex exists, and that its efferent pathway is through the sympathetic system.[5, 22-24] For this reason we tried to sever the pulmonary connections of the sympathetic ganglia on one side. This resulted in a greater resistance to the development of pulmonary edema, which was demonstrated by the small amount of foam present when greater than standard amounts of fluid were injected.‡ The uncertain result of the comparative study of the operated and intact side is not surprising when one considers the possibility of local causes of

*Extreme bradycardia has to be considered only in those experiments where the distention of the carotid sinus was not accompanied by infusion.

†The denervation of other organs can be accomplished only with open thorax. Artificial respiration necessary in this procedure inhibits the development of edema.

‡Bilateral stellate ganglionectomy was performed on two dogs subsequent to the preparation of this manuscript. The pleural cavity was not entered. Of the two dogs, one had the average pulmonary edema which may have been favored by a severe bradycardia during the infusion periods. The other dog had a minimal foam and an index of 1.3.

error, the multiplicity of nerve fibers, and the fact that sympathetic fibers going to the lungs are partly ipsilateral and partly contralateral.

Stimulation of nerve fibers which are anatomically sympathetic may favor the edema in two different ways: (1) by causing dilatation of the capillaries (it should be remembered that sympathetic vasodilators are cholinergic[25]); and (2) by directly increasing the permeability of the capillaries, independent of changes produced in the caliber of the vessels. This fact has been demonstrated in the case of the knee joint and was thought to be probably true for the lungs as well.[26, 27]

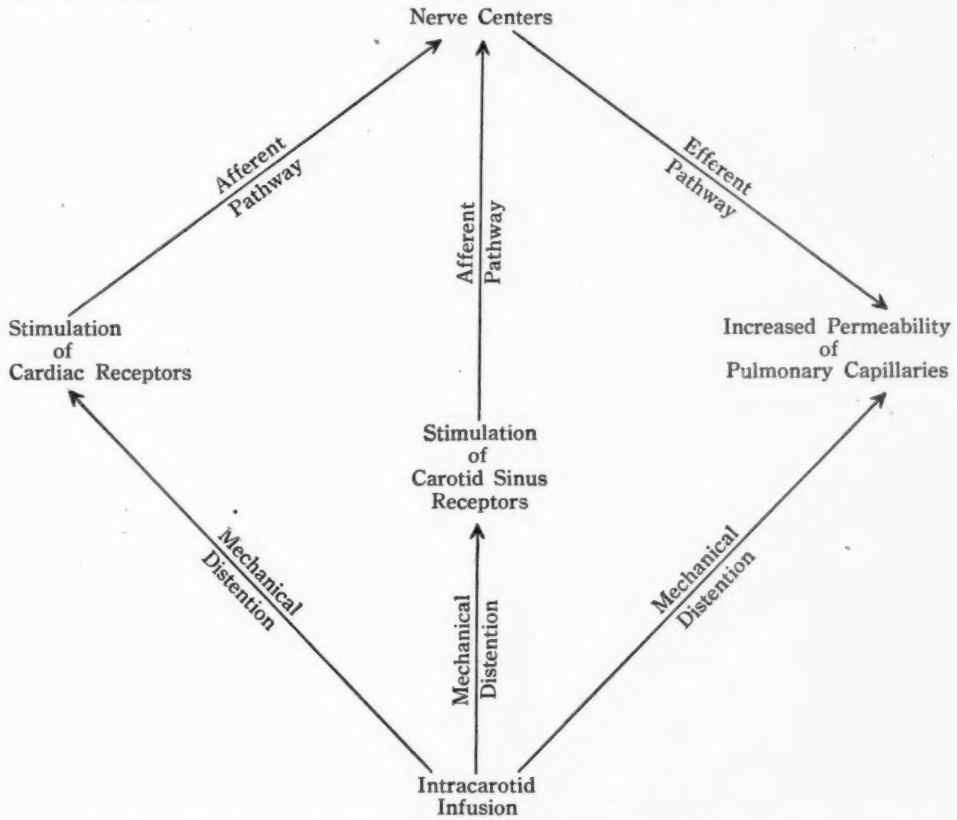


Fig. 1.—Diagrammatic representation of the mechanical and nervous factors which combine to produce the pulmonary edema experimentally induced by intracarotid infusion.

Cutting the vagus nerves, which has been found to increase pulmonary edema produced by venous infusion in cats and rabbits,[28, 29] did not increase pulmonary edema in our dogs. It likewise did not prevent the production of pulmonary edema by intracarotid infusion.

Stimulation of either the intact vagi or the peripheral end of the cut vagi caused pulmonary edema when the procedure was alternated with venous infusions. We are inclined to attribute this favoring action of the nervous stimulation to the resulting tremendous bradycardia, which at times approached

asystole. It is known that bradycardia favors congestion of the pulmonary vessels.[28, 31-34]

The importance of glottis spasm and possible bronchospasm in favoring pulmonary edema has been kept in mind. We have frequently seen spasm of the glottis accompanied by two or three deep abortive gasps which caused severe suction on the alveolar wall and on the wall of the lung capillaries. Experiments with rhythmic suction exerted on the trachea have shown that this leads to early and intense edema. However, even if spasm of the glottis favors the edema, it is not the main factor involved since tracheotomy does not diminish the edema. It is difficult to evaluate bronchospasm which is detected by auscultation, as a cause of a similar suction during inspiration.

The importance of the pressure existing in the bronchi and alveoli was first demonstrated in adrenalin-produced pulmonary edema,[35-38] then in pulmonary edema produced by ligature of the aorta,[39] and later in pulmonary edema caused by poison gas.[40] Our experiments have shown that either a rhythmic or a continuous increase of intratracheal pressure leads to inhibition of the edema. As our type of experimental edema is comparable to the extremely sudden and lethal type of human pulmonary edema, our experiments confirm the opinion that positive pressure may be useful in this syndrome.[38, 40] The action of the expiratory valve is probably more of a factor in experimental animals, which are strong and vigorous, than in patients, whose expiratory muscles may be unable to overcome the obstacle.

SUMMARY

The part played by mechanical and neurogenic factors in pulmonary edema experimentally produced in dogs by the use of a standard technique has been investigated. The basis of this standard technique is the rapid, interrupted infusion of saline solution into the carotid arteries toward the brain.

1. The quantity of injected fluid may be considered as submaximal, in the sense that, while the fluid favors the development of edema by distending the pulmonary vessels, the amount of fluid administered is insufficient of itself to produce edema.

2. The importance of specific receptors of the cardiovascular apparatus has been demonstrated. Their stimulation causes a reflex leading to increased permeability of the pulmonary capillaries, and favors the development of edema if these vessels are already distended. The problem of whether the reflex causes first a dilatation of the vessels, or whether its effect is the result of a direct increase of permeability needs further study. The most important among these reflexes is the carotido-pulmonary reflex whose afferent pathway to the central nervous system is through the glossopharyngeal nerve, and whose efferent pathway to the lungs is through fibers which are anatomically part of the sympathetic system. Another important reflex is that elicited by distention of the heart chambers. A third reflex, whose importance cannot yet be measured, is the pulmonary artery-pulmonary vessels reflex. All these reflexes are able to cause pulmonary edema when a submaximal quantity of fluid, in itself insufficient to produce edema, is injected into the circulation.

3. Deeper understanding of the mechanism can be obtained only by using drugs either to enhance or to inhibit the edema, and by studying by means of biologic assay the properties of both the blood and the edema fluid.

4. Electrical stimulation of either the cardiac end of the cut vagi or the intact nerves favors pulmonary edema by causing extreme bradycardia. This factor, however, does not play any role in the experiments of infusion with standard technique.

REFERENCES

1. Luisada, A. A., and Sarnoff, S. J.: Studies on Paroxysmal Pulmonary Edema: A New Experimental Method, Proc. Soc. Exper. Biol. & Med. **57**: 279, 1944. Also: Paroxysmal Pulmonary Edema Consequent to Stimulation of Cardiovascular Receptors. I. Effect of Intra-Arterial and Intravenous Infusions, AM. HEART J. **31**: 270, 1946.
2. Cyon de, E.: Les Nerfs du Coeur, Paris, 1906, Félix Alcan.
3. Bainbridge, F. A.: The Influence of Venous Filling Upon the Rate of the Heart, J. Physiol. **50**: 65, 1915.
4. Sassa, K., and Miyazaki, H.: The Influenc eof Venous Pressus Upon the Heart Rate, J. Physiol. **54**: 203, 1920.
5. Nonidez, J. F.: Identification of the Receptor Areas in the Venae Cavae and Pulmonary Veins Which Initiate Reflex Cardiac Acceleration (Bainbridge Reflex), Am. J. Anat. **61**: 203, 1937.
6. McDowall, J. S.: A Right Auricular Pressor Reflex, J. Physiol. **85**: 5P, 1934.
7. McDowall, R. J. S.: The Nervous Control of the Blood Vessels, Physiol. Rev. **15**: 98, 1935.
8. Brunelli, B.: Contributo Sperimentale Allo Studio del Regime Tensivo nel Piccolo Circolo, Fisiol. e med. **4**: 781, 872, and 886, 1933.
9. Brunelli, B.: Sulla Probabile Esistenza di Nuove Zone Vasosensibili Reflessogene, Arch. di farmacol. sper. **56**: 557, 1933.
10. Schwiegk, H.: Der Lungenentlastungsreflex, Pflüger's Arch. f. d. ges. Physiol. **236**: 206, 1935.
11. Daly de B., I., and Verney, E. B.: The Localization of Receptors Involved in the Reflex Regulation of the Heart Rate, J. Physiol. **62**: 330, 1927.
12. Heymans, C.: The Pressoreceptive Mechanism for the Regulation of Heart Rate, Vasomotor Tone, Blood Pressure and Blood Supply, New England J. Med. **219**: 147, 1938.
13. Parin, V. V.: Pulmonary Hemodynamic Reflexes, Am. Rev. Soviet Med. **1**: 251, 1944.
14. Cataldi, G. M.: Oedème Aigu du Poumon dans les Lésions Expérimentales du Ventricule Droit, Arch. d. mal. du cœur. **28**: 604, 1935.
15. Rubino, A.: Il Volume del Fegato durante la Necrosi Sperimentale del Ventricolo Destro e del Ventricolo Sinistro, Folia med. **23**: 1166, 1937.
16. Jarisch, A.: Vom Herzen ausgehende Kreislaufreflexe, Arch. f. Kreislaufforsch. **7**: 260, 1940.
17. Hochrein, M.: Klinische Probleme des Lungenkreislaufes, Arch. f. Kreislaufforsch. **14**: 24, 1938.
18. Heymans, C., Bouckaert, J. J., and Regniers, P.: Le Sinus Carotidien et la Zone Homologue Cardio-Aortique, Paris, Doin, 1933.
19. Thomas, C. B., and Brooks, C. M.: The Effect of Sympathectomy on the Vasomotor Carotid Sinus Reflex of the Cat, Am. J. Physiol. **113**: 130, 1935.
20. Thomas, C. B., and Brooks, C. M.: The Effect of Sympathectomy on the Vasomotor Carotid Sinus Reflex of the Cat, Am. J. Physiol. **120**: 195, 1937.
21. Daly de Burgh, I.: Reactions of the Pulmonary and Bronchial Blood Vessels, Physiol. Rev. **13**: 149, 1933.
22. Hochrein, M., and Keller, C. J.: Die Lunge ein Blutdepot, Klin. Wchnschr. **13**: 1383, 1934.
23. Hochrein, M.: Der Lungenkreislauf unter normalen und pathologischen Verhältnissen, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. p. 51, 1935.
24. Jarisch, A., Richter, H., and Thoma, H.: Zentrogenes Lungenoedem, Klin. Wchnschr. **18**: 1440, 1939.
25. Dale, H. H.: Nomenclature of Fibres in the Autonomic Nervous System and Their Effect, J. Physiol. **80**: 108, 1933.
26. Engel, D.: The Influence of the Sympathetic Nervous System on the Capillary Permeability, J. Physiol. **99**: 161, 1941.
27. Engel, D.: The Influence of the Sympathetic Nervous System on Capillary Permeability in Traumatic Shock, J. Physiol. **102**, 281, 1943.
28. Kraus, F.: Ueber Lungenoedem, Ztschr. Exper. Path. **14**: 402, 1913.

29. Farber, S.: Neuropathic Pulmonary Edema, Further Observations, Arch. Path. **30**: 180, 1940.
30. Brunn, F.: Experimentelles zum Lungenoedem, Wien. klin. Wchnschr. **46**: 262, 1933.
31. Hall, H. L.: Study of Pulmonary Circulation by Transillumination Method, Am. J. Physiol. **72**: 446, 1925.
32. Weber, E.: Ueber Aktive Aenderungen der Arteriellen Blutfuelle der Lungen, Arch. f. Phys. Suppl. Bd. 377, 1911; 383, 1912.
33. Cloetta, M.: Beitraege zur Physiologie u. Pathologie der Lungencirculation und deren Bedeutung fuer die Intrathoracale Chirurgie, Arch. f. Klin. Chir. **98**: 835, 1912.
34. Anderes, E., and Cloetta, M.: Eine Weitere Methode zur Pruefung der Lungenzirkulation, Arch. f. exper. Path. u. Pharmakol. **79**: 291, 1916.
35. Emerson, H.: Artificial Respiration in the Treatment of Edema of the Lungs, Arch. Int. Med. **3**: 368, 1909.
36. Auer, J., and Gates, F. L.: Experiments on the Causation and Amelioration of Adrenalin Pulmonary Edema, J. Exper. Med. **26**: 201, 1917.
37. Johnson, S.: The Experimental Production and Prevention of Acute Edema of the Lungs in Rabbits, Proc. Soc. Exper. Biol. & Med. **25**: 181, 1927-1928.
38. Barach, A. L., Martin, J., and Eckman, M.: Positive Pressure Respiration and Its Application to the Treatment of Acute Pulmonary Edema, Ann. Int. Med. **12**: 754, 1938.
39. Antoniazzi, E.: Ricerche Sperimentali sui Fattori Meccanici e Nervosi dell' Edema Polmonare Meccanico, Arch. per le sc. med. **54**: 818, 1930.
40. Barach, A. L.: The Treatment of Pulmonary Edema Due to Gas Poisoning in War and in the Civilian Life, New England J. Med. **230**: 216, 1944.

PAROXYSMAL PULMONARY EDEMA CONSEQUENT TO STIMULATION OF CARDIOVASCULAR RECEPTORS

III. Pharmacologic Experiments

Aldo A. Luisada, M.D., and Stanley J. Sarnoff, M.D.
Boston, Mass.

A NEW method for inducing acute pulmonary edema in dogs has been described in previous publications.[1, 2] The method is based upon the rapid intracarotid infusion of physiologic salt solution cephalad. A quantity of fluid equivalent to more than twice the estimated blood volume of a dog is injected within twenty minutes, in three separate portions, at a pressure of 280 to 300 mm. of mercury. This method almost always results in the production of very severe pulmonary edema (nine out of ten dogs in the control series showed severe pulmonary edema). Different types of fluid, including Ringer's, Tyrode's, bovine albumin solution, and dog blood were successively studied. It has also been shown that infusion into other vessels by the same technique does not cause pulmonary edema with the same consistency as does infusion into the carotid arteries.[2]

In a former communication[3] the relation of different mechanical and neurogenic factors to pulmonary edema were studied. The beneficial action of artificial respiration under positive pressure was demonstrated. The most striking procedure for the prevention of edema of the lungs was denervation of the carotid sinuses prior to the infusions. Cutting of the vagus nerves did not change the outcome. The conclusion reached was that acute pulmonary edema caused by the rapid intracarotid infusion of physiologic solutions is a syndrome which is only indirectly caused by the flooding of the circulatory system. The quantity of fluid introduced is submaximal and does not per se produce pulmonary edema. The increased fluid volume does place a heavy strain on the organs of the circulatory system and initiates multiple reflexes. Among these, a carotid sinus-pulmonary reflex is of paramount importance. A cardiopulmonary reflex is also significant. The afferent stimuli follow different routes; the efferent stimuli reach the lungs along sympathetic fibers.

It was thought that pharmacologic experiments might yield additional information as to the mechanism of this type of experimental pulmonary edema and also suggest the best treatment of this paroxysmal syndrome. These experiments are the subject of this paper.

Previous investigation of the treatment and prevention of acute pulmonary edema has been chiefly through clinical studies. A review of these studies was

From the Surgical Research Laboratory, Beth Israel Hospital and the Laboratory of Pharmacology, Tufts College Medical School, Boston, Massachusetts. The study was aided by grants by Ciba Pharmaceutical Products, Inc., and Hoffman-La Roche Inc. Presented in part before the New England Heart Association, Boston, Jan. 29, 1945.

Received for publication June 9, 1945.

published in 1942 by one of the authors (A. A. L.).[4] In 1928, one of the authors (A. A. L.) systematically studied treatment of pulmonary edema induced in rabbits by the intravenous injection of a massive dose of adrenalin.[5] There followed a study by Antoniazzi[6] on the pulmonary edema of rabbits caused by ligation of the aortic arch. Sporadic experiments were made by Brunn,[7] using luminal, and by Farber,[8] using atropine.

TABLE I

DRUG	SOLUTION (%)	DOSES (MG./KG.)	REMARKS
Morphine sulfate	1-6.5	3-32	-
Sodium phenobarbital	2	25-100	-
Sodium barbital	5	100-350	-
Chloral hydrate	5	150-290	-
Atropine sulfate	0.01-0.1	0.04-0.8	-
Scopolamine hydrobromide	0.1	0.3-0.5	-
Demerol, Winthrop	1	25-40	-
Syntropan, Roche	0.5	1.5-2	-
Trasentine hydrochloride, Ciba	5	2.5-3	-
Papaverine hydrochloride, Lilly	15-50	5-30	-
Curare (Intocostrin, Squibb)	0.5-1	1.35-1.8	-
Sodium nitrate	5	60	-
Acetyl-β-methylcholine (Mecholyl, Merck)	1	0.14-1.5	-
Physostigmine hydrochloride	0.1	1-4	High doses only in association with atropine
Prostigmine, Roche	0.1	0.05-1	High doses only in association with atropine
Procaine, Abbott	5	20-100	-
Nupercaine, Ciba	0.06	1.6	-
Ergotamine tartrate (Gynergen, Sandoz)	0.1	0.2-0.4	-
2-diethylamino-ethyl-1,4-benzodioxan (883 F—Soc. Parisienne Expans. Chim.)	-	4.5-9	-
Quinine dihydrochloride	5	25-70	-
Mercupurin, Campbell	10	10	In association with aminophylline
Aminophylline, Searle	5	54	-
Pitressin, Parke-Davis	-	2.7 units	-
Adrenalin hydrochloride (Suprarenalin, Armour)	0.01-0.00001	0.3-0.5	-
Metrazol, Bilhuber-Knoll	10	20	-
Coramine, Ciba	25	30	-
Cedilanid, Sandoz	-	0.5 (cat units)	-
Digiglusin, Lilly	-	0.5 (cat units)	-
Strophosid, Sandoz	-	0.33-0.36 (cat units)	

TECHNIQUE

The present study was made on 98 mongrel dogs. The technique of infusion into the carotid arteries is that described previously.[1] The fluid used in these experiments was 0.85 per cent sodium chloride solution. The injection of drugs was nearly always made into an exposed jugular vein. Exceptions will be reported in the sections dealing with the results. In nearly all experiments the anesthesia was that previously described[1] and called "standard"; namely, morphine sulfate (3 mg. per kilogram of body weight), injected subcutaneously,

and urethane (1 to 1.3 Gm. per kilogram of body weight), given by stomach tube thirty to sixty minutes later. The relatively small number of experiments performed with each drug allowed definite conclusions because of the fact that physiologic salt solution, infused by the technique described, almost without exception produced severe pulmonary edema in control animals.[2]

RESULTS AND COMMENTS

Hypnotics.—Animals given large doses of morphine prior to the infusion differed markedly from the controls, which in accordance with the standard technique were given only three mg. of morphine sulfate per kilogram of body weight. After large doses of morphine the dogs subjected to infusion gave evidence of only mild dyspnea and showed no agitation and no spasm of the glottis. The *lung/body index** was only slightly increased, and only a trace of foam was found in the dependent lobes of the lungs (Table II). Therefore, morphine is of definite value in preventing pulmonary edema induced by this standard technique, even if not completely successful.

TABLE II. HYPNOTICS

NO.	DRUG USED FOR ANESTHESIA	HYPNOTIC IN MG./KG. AND ROUTE	LUNG/BODY* INDEX	GRADE† OF EDEMA
12		Morphine, 30 subcutaneous and intravenous	1.40	+
120	Urethane, standard‡	Morphine, 30 subcutaneous and intravenous	1.34	+
13	Morphine, standard‡	Phenobarbital, 59 intravenous	1.63	+
121	Morphine, standard	Phenobarbital, 100 intravenous	1.06 (Incomplete infusion)	-
125	Morphine, standard	Phenobarbital, 70 intravenous	1.05	-
6	Morphine, 10 mg./kg.	Phenobarbital, 25 intravenous	1.25	-
152	Morphine, 15 mg./kg.	Phenobarbital, 40 intravenous	1.08	+
24	Morphine, standard	Barbital, 220 intravenous	1.35	-
29	Morphine, standard	Barbital, 100 intravenous	2.68	+++
122	Morphine, standard	Barbital, 350 intravenous	1.25	-
153	Morphine, 16 mg./kg.	Barbital, 125 intravenous	1.20	-
123	Morphine, standard	Chloral hydrate, 230 intravenous	1.38	-
124	Morphine, standard	Chloral hydrate, 230 intravenous	1.11	-
154	Morphine, standard	Chloral hydrate, 290 intravenous	0.96	-
151	Morphine, 13 mg./kg.	Chloral hydrate, 150 intravenous	1.75	++
187	Morphine, 8.5 mg./kg.	Chloral hydrate, 260 intravenous	1.20	+

*The lung/body index is the ratio of lung weight in grams to body weight in kilograms.

†The severity of the edema is graded from + to ++++ on the basis of the lung/body index and of the amount of foam.[2]

‡Standard doses used for anesthesia have been given under "technique."

Next, two barbiturates, phenobarbital and barbital, were studied. The sodium salt of each was given intravenously. Owing to the narcotic action of these drugs, we dispensed with the use of urethane. Both drugs completely prevented edema in four of six dogs. The fifth dog showed only a trace of edema, and the sixth, which exhibited more edema, had received a much smaller dose of barbital. None of the dogs had severe dyspnea, and in some experiments the *lung/body index* was normal. The combination of morphine with barbiturates, which was tried in three additional experiments, with similar positive

*The *lung/body index* is the ratio of lung weight in grams to body weight in kilograms.

results, allowed a marked decrease in the dose of barbiturates. It was found that the optimal dose of the single drugs per kilogram of body weight was about 70 to 100 mg. of sodium phenobarbital and 220 to 300 mg. of sodium barbital.

Doses of 230 to 300 mg. of chloral hydrate per kilogram of body weight completely prevented pulmonary edema in four of five dogs. Combination of this drug with morphine was also successful if the dose of chloral hydrate was not decreased too much. Chloral hydrate was interesting because it was effective in amounts which are comparable to those used clinically.

We used hypnotics in experiments on sixteen dogs. In spite of the varying doses which we used in seeking the optimum, severe pulmonary edema developed in only one dog, mild pulmonary edema developed in a second, and minimal edema developed in five more. That nine of the sixteen animals had no trace of edema is striking when compared with the very high percentage of animals in the control series[2] (approximately nine-tenths) which showed severe pulmonary edema.

Local Anesthetics.—Procaine was injected in doses of 30 to 60 mg. per kilogram of body weight either subcutaneously or by intracarotid or intrajugular injection. When the subcutaneous route was used, part of the dose was injected before and part between the infusions. The results of early experiments seemed satisfactory, but in later experiments the outcome was inconstant. Five out of 13 dogs died of severe pulmonary edema, three had high lung/body indices, with almost no foam, and three had no edema (Table III). It was concluded that some of the properties of procaine were useful, but that others promoted the edema. Depression of the excitability of the pressoreceptors should help in preventing this type of experimental pulmonary edema. Two actions of local anesthetics which most often promote the edema are: (a) sensitization of the vessels to the action of adrenalin and (b) stimulation of the cortex of the brain.

TABLE III. LOCAL ANESTHETICS

SERIAL NUMBER OF EXPERIMENT	DRUG	ROUTE OF ADMINISTRATION	DOSE (MG./KG.)	ASSOCIATE DRUG AND DOSE (MG./KG.)	INDEX LUNG/BODY	GRADE OF EDEMA
62	Procaine	Subcutaneously	30	–	1.68	+
63	Procaine	Subcutaneously	60	–	1.29	–
69	Procaine	Subcutaneously	60	–	2.9	+++
70	Procaine	Subcutaneously	40	–	4.35	++++
71	Procaine	Subcutaneously	32	–	1.34	–
75	Procaine	Subcutaneously	30	–	1.89	+
76	Procaine	Subcutaneously	60	Ergotamine tartrate, 0.3	2.52	+++
131	Procaine	Intracarotid	100	–	1.41	+
132	Procaine	Intracarotid	60	Morphine sulfate, 10		Early death
133	Procaine	Intravenous	60	–	1	–
134	Procaine	Intravenous	60	–	2.4	++++
135	Procaine	Intravenous	20	Sodium barbital, 70		Early death
162	Procaine	Lumbar	2.5	–	3.66	++++
171	Nupercaine	Subcutaneously	1.6	–	4.1	++++

The addition of either ergotamine, barbital, or morphine to the procaine did not seem to affect the results. The fact that all early deaths were accompanied by convulsions confirmed the impression that cortical stimulation was present and that the tolerance of the brain centers to the abnormal conditions imposed by the high pressure infusions was decreased. The convulsions were more severe when the injection of the drug was intravascular than when it was subcutaneous. In one experiment with spinal anesthesia, the edema was severe. Nupercaine, tried in another experiment, did not prevent severe edema from occurring.

Autonomic Blocking Drugs.—Atropine was first investigated. Five experiments were performed, with doses varying between 0.04 mg. and 0.8 mg. per kilogram of body weight. The outcome was consistently poor. The animals had more severe pulmonary edema than usual, so that the lungs weighed from three to five times more than normal. The combination of atropine and morphine was used in two experiments. This combination prevented pulmonary edema in one dog, but was not effective in the second animal (Table IV). Although the substitution of scopolamine for atropine, in doses varying between 0.3 mg. and 0.75 mg. per kilogram body weight produced somewhat better results, they were not comparable to those attained with other more beneficial drugs (Table IV).

A comparison of the effects of the various drugs leads one to attribute the poor results in the atropinized dogs mainly to drug stimulation of the nerve centers, which favored the functioning of reflexes. It might also be mentioned that after the administration of atropine, sympathetic reflexes became more active. In the light of the experimental results mentioned, the beneficial in-

TABLE IV. AUTONOMIC BLOCKING DRUGS

SERIAL NUMBER OF EXPERIMENT	DRUG	DOSE (MG./KG.)	ASSOCIATE DRUG AND DOSE (MG./KG.)	INDEX LUNG/BODY	GRADE OF EDEMA
9	Atropine	0.8	Morphine, standard	4.63	++++
21	Atropine	0.3	Morphine, standard	4.92	++++
87	Atropine	0.04	Morphine, standard	1.98	++
116	Atropine	0.05	Morphine, 15	1.26	-
117	Atropine	0.05	Morphine, 15	3.33	++++
144	Scopolamine	0.5	Morphine, standard	1.53	+
146	Scopolamine	0.75	Morphine, standard	2.75	+++
147	Scopolamine	0.3	Morphine, standard	1.90	+++
42	Ergotamine	0.2	Morphine, standard	1.92	+
47	Ergotamine	0.4	Morphine, standard	1.93	+
48	Ergotamine	0.3	Morphine, standard, and atropine, 0.25	1.80	++
20	883 F	9.0	Morphine, standard	1.24	Incomplete infusion
36	883 F	8.0	Morphine, standard	1.0	+
49	883 F	4.5	Morphine, standard, and atropine, 0.35	3.27	++++
14	Curare (Intocostrin)	1.8	Morphine, standard	1.4	Artificial respiration
79	Curare (Intocostrin)	1.6	Morphine, standard	1.7	+
126	Curare (Intocostrin)	1.35	Morphine, standard, and nembutal, 4.5	1.29	+

fluence of atropine in human pulmonary edema[4] should certainly be questioned. As far as the mechanism of the attack is concerned, the above experiments show that vagus stimulation is not one of the direct causes of the edema and may even counteract those stimuli which more directly favor the increased permeability of the lung vessels. Among the vagal reflexes which may normally protect the lung vessels, the pulmonary hemodynamic reflex[15-17] is probably the most important.

Two sympatholytic drugs were tried, ergotamine tartrate and 883 Fourneau (2-diethylamino-ethyl-1,4-benzodioxan).[22] Both acted favorably in the type of pulmonary edema which we are studying. It is interesting to note that dogs treated with ergotamine developed very little foam, though their *lung/body index* was rather high in comparison to that of normal dogs. On the contrary, 883 Fourneau seemed to prevent both the formation of foam and the high index (Table IV).

Both drugs may cause premature death of the animals during the infusion because of the extreme bradycardia which may progress to cardiac standstill. Knowing that severe bradycardia per se favors lung congestion,[2] one may ask whether this fact alone can explain the high index. The addition of atropine did not improve the results, and in one experiment produced poorer results. However, since the poor results of atropine are probably due to central stimulation, this fact is not surprising.

Curare gave excellent results when used in large amounts. However, the use of this drug required positive pressure artificial respiration, which alone is sufficient to prevent this type of pulmonary edema. A smaller dose of curare produced fair results. An even smaller dose in combination with a small dose of nembutal* produced good results. We have concluded that curare helps to

TABLE V. ANTISPASMODIC AND DEPRESSANT DRUGS

SERIAL NUMBER OF EXPERIMENT	DRUG	DOSE (MG./KG.)	ANESTHESIA	INDEX LUNG/BODY	GRADE OF EDEMA	REMARKS
172	Papaverine	15	Standard	2.1	++	-
176	Papaverine	30	Standard	2.7	+++	-
158	Papaverine	5	Standard	1.16	-	-
137	Demerol	40 subcutaneous	Urethane standard	-	-	Premature death
138	Demerol	30 subcutaneous	Urethane, standard	0.9	++	Abdominal hemorrhage
139	Demerol	25 intravenous	Standard	1.74	++	-
136	Syntropan	2 intravenous	Standard	-	-	Premature death
140	Syntropan	1.5 intravenous	Standard	1.17	-	-
141	Syntropan	1.5 intravenous	Standard	1.96	++	-
179	Trasentine	3 intravenous	Standard	1.04	+	-
182	Trasentine	3 intravenous	Standard	1.11	+	-
186	Trasentine	2.5 intravenous	Morphine mg. 10/kg.	2.12	+++	-
39	Quinine	70	Standard	2.7	+++	-
143	Quinine	25	Standard	2.51	+++	-

*Nembutal and curare have a synergistic action as far as the central nervous system is concerned.[23]

prevent pulmonary edema, probably because the central and gangliar depression produced by this drug limits the intensity of the reflexes. Further studies with curare will be reported upon later.

Antispasmodic and Depressant Drugs.—Papaverine did not seem to exert any beneficial action in preventing pulmonary edema in our experiments. However, since a combination of papaverine and morphine gave good results, it is possible that papaverine may enhance the favorable action of morphine.

Demerol did not seem as valuable as morphine. A large dose of demerol caused premature death from tonicoclonic contractions of the muscles as soon as the infusion was started; smaller doses, on the other hand, did not prevent the pulmonary edema. We had the impression that demerol stimulated the brain centers, and mainly the respiratory center, an action which favors the onset of pulmonary edema. Syntropan gave better results than demerol, but tonicoclonic contractions, which give evidence of cortical hyperexcitability, were again observed.

Trasentine seemed the best of the series. We had favorable results in two of three experiments. Quinine, on the contrary, did not confer any protective effect.

TABLE VI. AUTONOMIC STIMULATING DRUGS

SERIAL NUMBER OF EXPERIMENT	DRUG	DOSE (MG./KG.)	ROUTE OF FLUID INFUSION	AMOUNT OF FLUID AS COMPARED WITH ESTIMATED BLOOD VOLUME*	INDEX LUNG/BODY	GRADE OF EDEMA
18	Mecholyl	1	Femoral veins	2	1.66	+++
184	Mecholyl	0.14	Carotid arteries	2.3	3.77	++++
22	Physostigmine	1.2	Carotid arteries	1	2.62	++++
156	Adrenalin	0.5	One carotid artery	2.1	4	++++
161	Adrenalin	0.5	One jugular vein	2.3	1.61	++
163	Adrenalin	0.4	Jugular veins	2.3	1.89	+++
170	Adrenalin	0.3	Carotid arteries	2.3	4	++++

*The blood volume was estimated as equal to 10 per cent of the body weight.

Autonomic Stimulating Drugs.—In our experiments, drugs stimulating the parasympathetic system either directly, like mecholyl, or indirectly, like physostigmine, caused early death during the infusion, by producing cardiac standstill. This was not surprising, since intracarotid infusion under high pressure stimulates the pressoreceptors of the carotid sinus. If no drug is given, slowing of the heart rate because of the carotid sinus reflex is soon compensated for by the antagonistic Bainbridge reflex, which distention of the large veins initiates by the infused fluid. When, on the contrary, either an acetylcholine-like substance (mecholyl) or a substance which inhibits the cholinesterase (physostigmine) is acting, the effects of stimulatin of the vagus nerve are increased and the intracarotid infusion is followed by a severe bradycardia and even by early death from pulmonary edema. The use of either drug leads to pulmonary edema even when venous infusion is used. This is easily explained, because stimulation of the peripheral end of the vagus nerve during venous infusion also consistently leads to pulmonary edema. This fact has already been discussed,[4] and it was observed that the favoring element is brady-

cardia, a hemodynamic factor which leads to dilatation of the pulmonary vessels. Consideration of direct action of acetylcholine in promoting edema of the lungs cannot be excluded, for, when injected intradermally, acetylcholine forms a wheal. However, experiments using physostigmine in combination with atropine disprove this hypothesis.

Adrenalin promotes the production of pulmonary edema by our standard method. This was proved by the fact that either addition of the drug to the fluid or its intravenous injection in graded doses led to an enormous formation of foam and to very high lung/body indices. Moreover, addition of adrenalin to the fluid led to pulmonary edema when infusion was made into the jugular veins. Adrenalin promotes increased venous return in dogs through dilatation of the hepatic veins.[28] This increased venous return, together with the stimulation of the myocardium and the increased peripheral resistance also caused by adrenalin, raises the pressure in the pulmonary vessels and dilates them. Stimulation of both the aortic and the carotid pressoreceptors in the intervals between infusions will increase the intensity and the duration of those reflexes which favor the development of pulmonary edema. On the other hand, if the distention of the ventricles favors the production of edema through reflexes, adrenalin may slightly counteract this part of the mechanism by stimulating the myocardium. It is further to be noted that if stimulation of the sympathetic nerves increases the capillary permeability, as recent studies indicate,[29] injection of adrenalin should produce the same result.

Hyper- and Hypotensive Drugs, Diuretics.—Experiments with sodium nitrate, a drug exerting a hypotensive and vasodilating action, resulted in a mildly beneficial action. The lung/body index was rather high in two out of three experiments, but the foam was scanty in all three (Table VII). This result may be attributed to a decrease of the venous return due to extreme dilatation of the peripheral arteries. The same action in moderating the severity of the edema was not developed by aminophylline, a vasodilator and diuretic drug, even when Mercupurin, a mercurial diuretic, was added (Table VII). The difference be-

TABLE VII. HYPER- AND HYPOTENSIVE DRUGS: DIURETICS

SERIAL NUMBER OF EXPERIMENT	DRUG	DOSE (MG./KG.)	WAY OF FLUID INFUSION	AMOUNT OF FLUID AS COMPARED WITH ESTIMATED BLOOD VOLUME	INDEX LUNG/BODY	GRADE OF EDEMA
157	Sodium nitrate	60	Carotid arteries	2.3	1.67	+
160	Sodium nitrate	40	Carotid arteries	2.3	1.65	+
180	Sodium nitrate	40	Carotid arteries	2.3	1.21	+
168	Metrazol	20	Carotid arteries	2.3	1.6	++
169	Metrazol	20	Carotid arteries	1.6	2	+++
				Early death		
174	Coramine	30	Carotid arteries	2.3	2.3	+++
173	Aminophylline	54	Carotid arteries	2.3	1.88	++
178	Aminophylline plus mercupurin	50	Carotid arteries	2.3	2.1	+++
181	Pitressin	2.7 Units	Carotid arteries	1.65	4	++++

TABLE VIII. DRUGS STIMULATING THE MYOCARDIUM

SERIAL NUMBER OF EXPERIMENT	DRUG	DOSE (CAT UNITS PER KG.)	INDEX LUNG/BODY	GRADE OF EDEMA
142	Strophosid	0.36	1.24	++
175	Strophosid	0.33	1.6	+
177	Strophosid	0.33	3.79	++++
145	Cedilanid	0.5	3.75	++++
159	Digiglusin	0.5	2.22	+++

tween the action of sodium nitrate and that of aminophylline may be explained by the facts that aminophylline is a stimulant of the central nervous system and exerts special action on the medulla, and that it stimulates also the chemoreceptors of the carotid and aortic bodies.

Metrazol and coramine did not seem to affect the outcome of the experiment, except for the fact that doses which were too large caused early death during the infusion (Table VII). Both drugs stimulate the nerve centers and especially the respiratory center.

Pitressin was tried in one experiment, which resulted in early death and enormous pulmonary edema. Even though pitressin may decrease both the caliber and the permeability[31] of the lung capillaries, its effect is not sufficient to prevent pulmonary edema. It is apparent that the peripheral constriction of the capillaries of the greater circulation and the decreased filtration of fluids into the tissues of the body and into the serous cavities caused by pitressin more than offset any favorable action of this drug. The depressive action of pitressin on the diuresis may also be expected to act unfavorably.

Drugs Stimulating the Myocardium.—We performed three experiments with a strophanthin preparation, strophosid, and two with two different digitalis preparations, cedilanid and digiglusin. The drugs were injected intravenously before cannulation of the arteries, i.e., about thirty minutes before the beginning of the first infusion. Digitalis preparations did not affect the outcome. Strophanthin seemed to exert a slightly beneficial action in preventing pulmonary edema. One of three dogs had a low lung/body index and one had relatively scanty foam. This result may be attributed to the fact that digitalis and digitalis-like glycosides stimulate the myocardium and decrease the distention of the ventricles when these are submitted to a severe strain. We have observed that ventricular distention may be consideerd as a secondary cause of the type of pulmonary edema we are studying, because it stimulates the ventricular receptors. Therefore, it seems logical that strophanthin would have a slightly beneficial action in preventing pulmonary edema. Should pulmonary edema be caused by failure of the left ventricle, a much more striking result would take place. The difference in action between the glycosides of strophanthus and those of digitalis is due to the fact that the former acts much more quickly.

Physostigmine or Prostigmine in Association With Protective Drugs.—As described in a previous paragraph, physostigmine promotes the development of the type of experimental pulmonary edema which we are studying. However, if atropine is added to physostigmine, the result is reversed (Table IX).

Of three dogs, two developed no pulmonary edema, and one (in the summer) had only a slight trace of foam.* The most probable explanation of these results is the following: (a) Physostigmine, used alone, produces pulmonary edema by causing extreme bradycardia and asystole. (b) If the bradycardia is prevented by atropine, the physostigmine is free to exert its central depressant action,[35, 36] which helps to prevent reflexes which favor pulmonary edema. The addition of another central depressant, morphine, gave very satisfactory results.

TABLE IX. PHYSOSTIGMINE OR PROSTIGMINE PLUS ALLIED DRUGS

SERIAL NUMBER OF EXPERIMENT	PHYSOSTIGMINE OR PROSTIGMINE (DOSE IN MG./KG.)	ATROPINE OR SCOPOLAMINE (DOSE IN MG./KG.)	CURARE OR MORPHINE (DOSE IN MG./KG.)	INDEX LUNG/BODY	GRADE OF EDEMA	REMARKS
19	Physostigmine 2	Atropine 0.2	-	1.15	-	-
26	Physostigmine 1.4	Atropine 0.17	-	1.09	-	-
107	Physostigmine 2	Atropine 0.5	-	1.75	+	Summer
118	Physostigmine 1	Atropine 0.1	Morphine 16	1.13	-	-
127	Physostigmine 3	Atropine 0.2	Curare 4	1.33	-	-
101	Prostigmine 0.5	Atropine 0.1	-	1.8	+	Summer
106	Prostigmine 0.05	Atropine 0.05	-	2.1	+	Summer
108	Prostigmine 0.25	Atropine 0.2	-	3.1	++++	Summer
129	Prostigmine 0.5	Atropine 0.3	-	1.12	+	Summer
148	Prostigmine 0.4	Scopolamine 0.3	-	2.54	+++	-
185	Prostigmine 0.8	Atropine 0.1	-	5	++++	-
119	Prostigmine 0.3	Atropine 0.1	Morphine 16	1.11	-	-
128	Prostigmine 0.9	Atropine 0.3	Curare 3	1.5	-	-
130	Prostigmine 0.8	Atropine 0.2	Curare 3	1.3	-	-
149	Prostigmine 1	Scopolamine 0.4	Curare 4.6	1.3	+	-
150	Prostigmine 0.8	Atropine 0.1	Curare 6	1.17	-	-

The considerations mentioned and the observation that large doses of physostigmine cause muscular twitchings and cramps which may even impair respiration led us to combine curare with physostigmine. As far as the peripheral nerves are concerned, the action of curare is antagonistic to that of physostigmine. Therefore, a combination of the two drugs should have no peripheral action whatsoever. However, curare has a depressant action on the ganglia and on the central nervous system[24, 25] which strengthens the central depression caused by prostigmine.[25] Very satisfactory results were obtained in experiments in which physostigmine, atropine, and curare were combined (Table IX). It should be observed, therefore, that the central and not the peripheral action of physostigmine is the more important factor in the prevention of pulmonary edema. As atropine, used alone, favors pulmonary edema, it is advisable to give only the amount of this drug necessary, and no more. Theoretically, atropine might be dispensed with whenever curare is added to physostigmine. However, curare prevents vagus action only in very large doses and this effect is transitory.[38] Therefore, in spite of the desirability of simplifying the experiments, a small dose of atropine is necessary.

Prostigmine should exert a central depressant action in smaller doses than physostigmine. For this reason it was tried, in combination with atropine, in doses from one-fourth to one-fortieth as large as those of physostigmine.

*The importance of environmental temperature has been discussed in previous papers.[2, 3]

These doses proved to be too small. However, when either morphine or curare was added, the results of the use of prostigmine were excellent (Table IX). We must conclude that prostigmine is not so effective in the prevention of pulmonary edema as physostigmine, but that it is just as effective when combined with other drugs having a depressant effect on the central nervous system (morphine, curare). In its favor are its efficacy in smaller doses and the more prolonged duration of its effect.

The excellent results obtained by the combination of a mixture of curare (or morphine) and physostigmine (or prostigmine) with a small protective dose of atropine are shown by the fact that, of seven dogs so treated before and during infusion, only one had even a minimal trace of pulmonary edema. The substitution of scopolamine for atropine does not offer any advantages.

Intravenous injection of curare-atropine-prostigmine in a normal unanesthetized dog was well tolerated. The only visible effects were immediate diarrhea and weakness of the limbs for a few minutes.

GENERAL CONSIDERATIONS ON THE MECHANISM OF PULMONARY EDEMA

As we have already stated in a previous publication,[3] pulmonary edema produced by our technique is the expression of a diffuse attempt quickly to get rid of the tremendous amount of fluid which is injected. However, this pulmonary manifestation is so important that it may bring about the death of the animal. That it has special features and a special mechanism are shown by the fact that the pulmonary edema may be prevented by various devices (bleeding, artificial respiration, denervation of the carotid sinus), at times without interfering with other features of the general syndrome. Pharmacologic studies throw further light on the mechanism of pulmonary edema. It is entirely possible to prevent the occurrence of this type of pulmonary edema by use of hypnotics. This confirms the hypothesis that a reflex mechanism, having its starting point mainly in the carotid sinus, and possibly also within the heart itself, favors the occurrence of the edema. The exact localization by the use of different hypnotics of the nerve centers involved did not prove successful. However, the fact that morphine had a useful action suggests involvement of the respiratory center, or at the least shows that the prevention of dyspnea is important, by excluding a mechanical factor favoring the edema. The beneficial action of chloral hydrate in preventing pulmonary edema cannot be explained by the fact that it produces secondary dilatation of the peripheral vessels. The action of the barbiturates points more to involvement of the brain stem in the mechanism of pulmonary edema. Further studies are suggested by the facts that stimuli initiated in the carotid sinus reach the brain along the glossopharyngeal nerve and that the center of the water metabolism, located in the middle brain, is probably playing an important role whenever the blood volume is more than tripled within a short time.

Parasympatholytic drugs had a harmful effect. The effect of atropine was more harmful than that of scopolamine. This indicates that a carotido-vagal reflex is not involved in pulmonary edema, and that moderate vagal stimulation

might even help in preventing the edema. On the other hand, extreme bradycardia is not a favorable factor in preventing the edema, because it tends to cause hyperemia of the lungs. The stimulation of the central nervous system caused by atropine and the slight depression caused by scopolamine may account for the slightly different results obtained by the use of these two drugs. The useful action of sympatholytic drugs such as ergotamine and 883 Fourneau suggests that a carotido-sympathetic reflex (and possibly a less important cardio-sympathetic reflex) are involved in the mechanism of the edema. This would not be surprising, for a carotido-sympathetic reflex has been found to be the cause of the fall in blood pressure which follows distention of the carotid sinus.[21] The inconstant results obtained with sympatholytic drugs may be explained by the fact that whenever unbalanced vagus action is allowed to take place, distention of the carotid sinus causes extreme bradycardia or even asystole. To discover whether a carotido-sympathetic reflex favors pulmonary edema through dilatation of the capillary vessels or through direct change of their permeability[29] we used vasodilator drugs (sodium nitrite, aminophylline). Sodium nitrite had a moderately beneficial effect. This fact, however, cannot either favor or disfavor any of the two possibilities, because on the one hand, peripheral vasodilation decreases the venous return and may prevent the edema; on the other hand, the pulmonary vasodilator action may increase the severity of the edema. The same may be said about pitressin, which decreased permeability but produced harmful results. The favorable action of curare is explained by the depressant effect of this drug on the brain centers and on the ganglia. That curare has this action is confirmed by the experiments in which the combination of curare with prostigmine gave definitely better results than the use of curare alone.

The actions of physostigmine and prostigmine, which have been discussed at length can be explained only by their depressant effect on the ganglia,[34] on the spinal cord,[35, 36] and on the brain[24, 25] and not by any cardiac or vascular effect.

Digitalis and digitalis-like glycosides were tried in order to study the suggestion of French authors that they might be useful.[33] The slightly beneficial action of strophanthin may be explained by the reduction in the size of the distended ventricles and by the consequent decreased stimulation of cardiac receptors. If cardiac failure were the cause of the type of experimental edema of the lungs which we are studying, the result would have been much more striking.

The pharmacologic experiments reported here confirm our previous interpretation[3] of the acute pulmonary edema brought about by our standard method. We believe that this general conclusion, which had been foreshadowed by results of experiments on pulmonary edema caused by adrenalin,[5] ligation of the aortic arch,[6] venous infusion,[7, 8] and suboccipital injection,[39] should now definitely focus the attention of students of pulmonary edema upon the nervous system and not upon the myocardium. That either irritation of the myocardium (coronary occlusion), or distention of the heart cavities (heart failure, hyper-

tension) may be one of the causes of pulmonary edema cannot be denied, but we feel that either of these phenomena is secondary to the distention of the large arterial vessels as a cause of reflexes which favor acute edema of the lungs. We should like to emphasize the word "favors." For the occurrence of pulmonary edema a condition of distention of the lung capillaries is essential. This distention is caused by the energetic work of both ventricles, as Sahli and Kotowschikow have ascertained, and requires high arterial pressure and/or high venous return, as Starling has demonstrated. On this condition, an acute reflex increase of permeability may be superimposed which will lead to paroxysmal edema. Any factor decreasing either the arterial pressure or the venous return will act against the possibility of the edema. Factors leading to a decreased distention of either the ventricular cavities or the arteries containing pressoreceptors will produce the same result. Any depressing effect either on the sensitive receptors, on the nerve centers, or on the autonomic pathways of the reflexes will also help prevent the edema.

General Considerations on the Prevention and the Therapeutics of Pulmonary Edema.—In our systematic study of the effect of drugs on experimental pulmonary edema the following drugs were found to be useful: (1) hypnotics; (2) prostigmine, in combination with either curare and atropine or morphine and atropine; (3) drugs inhibiting the sympathetic system; and (4) less constant results were obtained with local anesthetics (novocaine) or trasentine.

That hypnotics would exert a beneficial action was foreseen from the results of previous experimental and clinical studies. Chloral hydrate alone and in combination with morphine seems to be the most promising for clinical applications. The action of prostigmine in combination with either morphine or curare has been described for the first time and may give favorable results in clinical applications. Novocaine may exert a favorable action, but should not be used in large doses. Trasentine deserves further study and may prove useful. Aminophylline, mercurial diuretics, and papaverine may be of general help in preventing edema, but proved ineffective if used in the imminence of an attack. Digitalis and strophanthin should also not be counted upon in the treatment of a paroxysmal attack of pulmonary edema. The following may be said of the clinical application of the two main groups of beneficial drugs: (a) Hypnotics may be used by intravenous injection, since their application by this route has been already tried both in normal individuals[39] and in clinical cases of pulmonary edema.[4] (b) Prostigmine and allied drugs should be tried first by subcutaneous injection. Intravenous administration may be superior, but should not be tried until it has been seen that possible secondary effects (bradycardia, bronchospasm, etc.) are not harmful.

SUMMARY

1. A systematic study of various drugs has been made in the treatment of acute experimental pulmonary edema caused by the rapid intracarotid infusion of physiologic salt solution.

2. The following drugs conferred protective effects and tended to prevent the development of edema:

a. The best results were obtained by hypnotics (phenobarbital, barbital, chloral hydrate) and by combination of any one of the hypnotics with morphine.

b. A combination of prostigmine with either atropine and curare or atropine and morphine also gave excellent results.

c. Sympatholytic drugs (ergotamine, 883 F), novocaine, and trasentine gave less constant results.

d. Vasodilators and drugs stimulating the myocardium only occasionally gave good results.

e. Atropine, adrenalin, and pitressin definitely made the edema of the lungs worse.

3. Observations on the pathogenesis of acute pulmonary edema caused by the method of rapid intracarotid infusions are drawn from the reported pharmacologic studies. Attention is called to the important part that the central nervous system plays in the syndrome and to reflexes leading to an acute increase of capillary permeability of the lungs.

4. Therapeutic considerations are drawn from the reported experiments.

We should like to acknowledge the helpful technical assistance of Salvatore N. Mangano and Michael M. Lovezzola.

REFERENCES

1. Luisada, A. A., and Sarnoff, S. J.: Studies on Paroxysmal Pulmonary Edema: A New Experimental Method, Proc. Soc. Exper. Biol. & Med. 57: 279, 1944.
2. Luisada, A. A., and Sarnoff, S. J.: Paroxysmal Pulmonary Edema Consequent to Stimulation of Cardio-Vascular Receptors. I: Effect of Intra-Arterial and Intravenous Infusions, AM. HEART J. 31: 270, 1946.
3. Luisada, A. A., and Sarnoff, S. J.: Paroxysmal Pulmonary Edema Consequent to Stimulation of Cardiovascular Receptors. II: Mechanical and Neurogenic Elements, AM. HEART J. 31: 282, 1946.
4. Luisada, A. A.: The Treatment of Paroxysmal Pulmonary Edema, Exper. Med. & Surg. 1: 22, 1943.
5. Luisada, A. A.: Beitrag zur Pathogenese und Therapie des Lungenödems und des Asthma cardiale, Arch. f. exper. Path. u. Pharmakol. 132: 313, 1928.
6. Antoniazzi, E.: Ricerche Sperimentali sui Fattori Meccanici e Nervosi dell Edema Polmonare Meccanico, Arch. per le sc. med. 54: 818, 1930.
7. Brunn, F.: Ueber Lungenoedem, Med. Klin. 30: 483 and 520, 1934.
8. Farber S.: Neuropathic Pulmonary Edema. Further Observations, Arch. Path. 30: 180, 1940.
9. Pick, E. P.: Schlaf und Schlafmittel, Wien, 1927, Julius Springer. Also: The Site of Action of Hypnotics and Analeptics in the Brain, J. Mt. Sinai Hosp. 7: 609, 1941.
10. Heymans, C., Bouckaert, J. J., and Regniers, P.: Le Sinus Carotidien et la Zone Homologue Cardio-Aortique, Paris, 1933, Gaston Doin & Cie.
11. Sarnoff, S. J., and Farr, H. W.: Spinal Anesthesia in Therapy of Pulmonary Edema, Anesthesiology 5: 69, 1944.
12. Vercauteren, E.: Recherches sur la Pharmacologie des Reflexes Vasomoteurs du Sinus Carotidien, Arch. internat. de pharmocodyn. et de thérap. 42: 339, 1932.
13. Heymans, C., Bouckaert, J. J., and Bert, P.: Mécanisme du Collapsus Circulatoire. Influence des Traumatismes et de la Rachianésthesie sur les Reflexes Circulatoires Sino-Carotidiens, Compt. rend. Soc. de biol. 112: 714, 1933.
14. Hirschfelder, A. D., and Tancales, G. : Inhibition of Experimental Auricular Fibrillation by Procaine and Other Substances, Proc. Soc. Exper. Biol. & Med. 50: 272, 1942.
15. Brunelli, B.: Contributo Sperimentale allo Studio del Regime Tensivo nel Piccolo Circolo, Fisiol. e med. 4: 781, 872, and 887, 1933.
16. Schwiegk, H.: Der Entlastungreflex, Pflüger's Arch. f. d. ges. Physiol. 235: 206, 1935.
17. Parin, V. V.: Pulmonary Hemodynamic Reflexes, Am. Rev. Soviet Med. 1: 251, 1944.
18. Dale, H. H.: On Some Physiological Actions of Ergot, J. Physiol. 34: 163, 1906.
19. Rothlin, E.: Ueber die pharmakologische und therapeutische Wirkung des Ergotamins auf den Sympathicus, Klin. Wchnschr. 4: 1437, 1925.

20. Heymans, C., and Regniers, P.: Influence de l'Ergotamine sur les Reflexes Cardio-Vasculaires du Sinus Carotidien, Arch. internat. de pharmacodyn. et de thérap. **36**: 116, 1929.
21. Thomas, C. B., and Brooks, C. M.: The Effect of Sympathectomy on the Vasomotor Carotid Sinus Reflex of the Cat, Am. J. Physiol. **113**: 130, 1935; **120**: 195, 1937.
22. Wright, S.: Action of Ergotamine on Vasomotor Reflexes, J. Physiol. **69**: 331, 1930.
23. Bacq, S. M., and Frédéricq, H.: Recherches sur la physiologie et la pharmacologie du système nerveux autonome. Modifications Apportées par Deux Dérivés de l'Amino-méthyl-benzodioxane (883 F. et 933 F.) aux Effets de l'Adrenaline et de l'Excitation Sympathique sur la Membrane Nictitante du Chat, Arch. intern. de physiol. **40**: 454, 1935.
24. Feitelberg, S., and Pick, E. P.: Action of Curare on the Brain of the Frog, Proc. Soc. Exper. Biol. & Med. **49**: 654, 1942.
25. Pick, E. P., and Unna, K.: The Effect of Curare and Curare-Like Substances on the Central Nervous System, J. Pharmacol. & Exper. Therap. **83**: 59, 1945.
26. Loewit, M.: Ueber die Entstehung des Lungenoedems; ein Beitrag zur Lehre vom Lungenkreislauf, Beitr. z. path. Anat. u. z. allg. Path. **14**: 401, 1893.
27. Grossmann, M.: Das Muscarin-Lungenoedem, Ztschr. f. klin. Med. **12**: 550, 1887.
28. Mautner, H., and Pick, E. P.: Ueber die durch Schockgifte erzeugten Zirkulationstoerungen, München. med. Wchnschr. **62**: 1141, 1915 (2d) and Biochem. Ztschr. **127**: 72, 1922.
29. Engel, D.: The Influence of the Sympathetic Nervous System on the Capillary Permeability, J. Physiol. **99**: 161, 1941.
30. Krogh, A.: Anatomie und Physiologie der Kapillaren, Berlin, 1924, Julius Springer.
31. Poulsson, L. T.: Ueber die exsudationshemmende Wirkung des Pituitrins, Arch. f. exper. Path. u. Pharmakol. **120**: 120, 1927.
32. Molitor, H., and Pick, E. P.: Zur Kenntniss der Pituitrinwirkung auf die Diurese, Arch. f. exper. Path. u. Pharmakol. **101**: 169, 1924.
33. Vaquez, H., and Lutembacher, R.: La Question de l'Ouabaine Arnaud, Presse méd. **36**: 129, 1928.
34. Feldberg, W., and Vartiainen, A.: Further Observations on the Physiology of a Sympathetic Ganglion, J. Physiol. **83**: 103, 1934.
35. Schweitzer, A., and Wright, S.: Action of Eserine and Related Compounds and of Acetylcholine in the Central Nervous System, J. Physiol. **89**: 165, 1937.
36. Schweitzer, A., Stedman, F., and Wright, S.: Central Action of Anticholinesterases, J. Physiol. **96**: 302, 1939.
37. Mautner, H., and Luisada, A. A.: Antagonistic Effect of Asphyxia to Curare Paralysis of the Vagus Nerve, J. Pharmacol. & Exper. Therap. **72**: 386, 1941.
38. Jarisch, A., Richter, H., and Thoma, H.: Zentrogenes Lungenoedem, Klin. Wchnschr. **18**: 1440, 1939.
39. Luisada, A. A.: Sulla Possibilità di Introdurre Narcotici per Via Endovenosa nell' Uomo, Riv. Ital. Terapia, N. 4, 1928.

THE COINCIDENCE OF AURICULAR FIBRILLATION AND BACTERIAL ENDOCARDITIS

ROGER K. MCDONALD, M.D.
MINNEAPOLIS, MINN.

THE belief that bacterial endocarditis and auricular fibrillation rarely coexist seems to be almost universal. Many cardiologists believe that bacterial endocarditis practically never develops in the presence of auricular fibrillation. It is the purpose of this paper to study the basis for this belief and to offer a possible explanation why auricular fibrillation occurs less frequently with bacterial endocarditis than with rheumatic heart disease. Those who contend that auricular fibrillation and bacterial endocarditis are rarely encountered together need not look far for support.

In 1923, Blumer[1] found four instances of auricular fibrillation among 301 patients with subacute bacterial endocarditis. In this study he noted, "These figures, however, are probably misleading, for many cases were recorded long before modern methods of pulse study were in vogue." In 1926, Thayer[2] reported that in 60 fatal cases of subacute bacterial endocarditis (streptococcic), in the main the result of myocardial insufficiency, four cases of auricular fibrillation were encountered. In neither of the above studies was there any mention of one process' developing before the other.

In 1927, Rothschild, Sacks, and Libman[3] reported a study of 123 patients with subacute bacterial endocarditis, 61 of whom had had electrocardiograms made. Among these 61 patients, auricular fibrillation was encountered in four. There was no evidence that auricular fibrillation was present in any of the 62 patients for whom no electrocardiograms were made. In one of the four cases with fibrillation the rhythm had been normal until three days before death. This was the only instance in the group in which fibrillation developed in an active case. In the other three patients, fibrillation developed in the bacteria-free stage. Basing their opinion upon the occurrence of auricular fibrillation in three of fourteen patients in the bacteria-free stage of bacterial endocarditis, they stated that the coexistence of these two pathologic processes was relatively common. These authors noted that, even in the presence of heart failure, the patients generally retain a normal rhythm. They also approached the problem from another aspect. In a study of 200 patients with auricular fibrillation selected at random, they found that none had, or developed, subacute bacterial endocarditis. They concluded, "The observation that auricular fibrillation and active subacute bacterial endocarditis are mutually exclusive (save in an exceptional instance) is of diagnostic value."

From the Department of Pathology, University of Minnesota.
Received for publication July 26, 1945.

In 1932, Fulton and Levine[4] reported that in a study of 111 patients with subacute bacterial endocarditis, auricular fibrillation was found only in one instance, where it developed as a terminal event. Of these 111 cases, 84 were hospital patients, and electrocardiograms were made on 62. They stated, "The inference to be drawn is that the heart remains essentially regular in subacute bacterial endocarditis, and, furthermore, if a patient had auricular fibrillation it is extremely unlikely that he had or ever will develop subacute bacterial endocarditis."

In 1933, Laws and Levine[5] noted that two of 43 patients with subacute bacterial endocarditis had auricular fibrillation. In one of these the auricular fibrillation was present before the onset of the subacute bacterial endocarditis, and in the other it occurred as a terminal event. In 1935, Segal[6] reported 192 cases of subacute and acute bacterial endocarditis. In this group, auricular fibrillation was encountered five times. In only one case did the auricular fibrillation precede the onset of the bacterial endocarditis. Finally, in 1941, Christian[7] reported that, in 150 cases of *Streptococcus viridans* endocarditis, only four patients were observed to develop auricular fibrillation.

In summarizing these seven studies, one finds that they include a total of 980 cases of bacterial endocarditis. In the total group, auricular fibrillation was present in 24 cases (2.45 per cent). Of these 24 patients with auricular fibrillation, in 11 fibrillation definitely began after the onset of bacterial endocarditis, in two auricular fibrillation definitely antedated the onset of bacterial endocarditis, and in 11 patients no mention was made of one process' occurring before the other.

SOURCE AND ANALYSIS OF MATERIAL

This paper is based upon a study of 286 cases of bacterial endocarditis. These all came to autopsy and were taken from the University of Minnesota Hospitals, Ancker Hospital of St. Paul, Minneapolis General Hospital, and various other hospitals in Minneapolis and St. Paul (Table I). In this series of 286 patients, 36 examples of auricular fibrillation were encountered (12.59 per cent).

TABLE I. SOURCES OF TWO HUNDRED AND EIGHTY-SIX CASES OF BACTERIAL ENDOCARDITIS AND PERCENTAGE INCIDENCE OF AURICULAR FIBRILLATION

HOSPITAL	CASES OF BACTERIAL ENDOCARDITIS	CASES OF AURICULAR FIBRILLATION	PERCENTAGE OF COINCIDENCE
University of Minnesota	62	5	8.06
Ancker	64	8	12.50
Minneapolis General	70	11	12.55
Others	90	12	13.33

Because the reports on many of the 90 cases from "Other Hospitals" were not complete, further analysis in this study has been confined to the 196 cases from the first three hospitals listed in Table I.

The distribution of the 196 cases of bacterial endocarditis in the various age groups, with the frequency of auricular fibrillation, is shown in Table II. Generally speaking, this disease is an affection of the younger age groups.

TABLE II. AGE DISTRIBUTION AND PERCENTAGE INCIDENCE OF AURICULAR FIBRILLATION IN ONE HUNDRED AND NINETY-SIX PATIENTS WITH BACTERIAL ENDOCARDITIS

AGE (YRS.)	NUMBER OF CASES OF BACTERIAL ENDOCARDITIS	PERCENTAGE OF TOTAL CASES	NUMBER OF CASES OF AURICULAR FIBRILLATION	PERCENTAGE INCIDENCE OF AURICULAR FIBRILLATION
0 to 9	6	3.06	1	16.67
10 to 19	20	10.20	0	0.00
20 to 29	53	27.04	7	12.96
30 to 39	41	20.92	4	9.76
40 to 49	32	16.33	3	9.38
50 to 59	28	14.29	5	17.86
60 to 69	10	5.10	3	33.33
70 to 79	3	1.53	0	0.00
80 to 89	3	1.53	1	33.33

It will be noted that the incidence of bacterial endocarditis reaches its peak in the third decade. The incidence of auricular fibrillation is higher in the older age group, reaching 20.5 per cent after the age of 50 years, as compared with 9.87 per cent up to the age of 50.

The sex incidence showed 88 women and 101 men. Seventy-five per cent of the women with bacterial endocarditis came to autopsy before the age of 40 years, while only 50 per cent of the men so affected were autopsied before this age. This observation would suggest that women develop active bacterial endocarditis at an earlier age.

The combinations of valvular involvement were studied in the 196 cases, and several interesting findings were noted. Table III shows the incidence of bacterial endocarditis and auricular fibrillation in the various combinations of valvular involvement.

TABLE III. THE INCIDENCE OF BACTERIAL ENDOCARDITIS AND AURICULAR FIBRILLATION IN RELATION TO VARIOUS VALVULAR INVOLVEMENTS

VALVES INVOLVED	NUMBER OF CASES OF BACTERIAL ENDOCARDITIS	PERCENTAGE OF CASES OF BACTERIAL ENDOCARDITIS	NUMBER OF CASES OF AURICULAR FIBRILLATION	PERCENTAGE INCIDENCE OF AURICULAR FIBRILLATION
Aortic and mitral	87	44.39	11	12.64
Mitral alone	80	40.82	9	11.25
Aortic alone	18	9.18	3	16.67
Tricuspid, aortic, and mitral	3	1.53	0	0.00
Tricuspid and aortic	1	0.51	0	0.00
Tricuspid, mitral, and pulmonary	1	0.51	0	0.00
Tricuspid alone	3	1.53	0	0.00
No valvular involvement	3	1.53	1	33.33

It is seen that involvement of both aortic and mitral valves on the one hand, and of the mitral valve alone on the other, were about equal. The incidence of auricular fibrillation in both groups was about the same: 12.64 per cent and 11.25 per cent, respectively. It is of especial interest that in the cases in which only the aortic valve was involved the incidence of auricular fibrillation was fully as high as in the cases with mitral involvement alone or combined aortic and mitral valvular involvement. In the patients in whom only the aortic

valve was involved, the mechanism producing auricular fibrillation was presumably based on a relative mitral insufficiency due to left ventricular dilatation.

The single example of auricular fibrillation with no valvular involvement occurred in an 8-year-old boy. This patient had a bacterial endocarditis superimposed on an active rheumatic carditis. The auricular fibrillation developed sometime after the onset of the bacterial endocarditis, but it persisted over a period of three and one-half months, until the death of the child.

Analysis of the Twenty-Four Cases of Auricular Fibrillation.—The fibrillation in 21 patients was persistent; in three it was of the paroxysmal variety. Congestive failure was present in all of the 21 patients with the persistent variety and in one of the three patients with paroxysmal fibrillation.

The following data in regard to the onset and duration of the fibrillation were observed: Of the three patients with paroxysmal auricular fibrillation, one had fibrillation during the thirteen days of hospitalization prior to death, one had fibrillation for the one day of hospitalization before death, and one had two observed paroxysms of fibrillation during thirty-three days of hospitalization prior to death. Of the 21 patients with persistent auricular fibrillation, five definitely developed fibrillation after bacterial endocarditis was present. Ten of the 21 patients showed both fibrillation and bacterial endocarditis at the time of admission, and therefore no statement can be made regarding the occurrence of one process before the other. In six, a persistent auricular fibrillation was definitely present before the bacterial endocarditis developed. These six cases in which auricular fibrillation preceded the onset of bacterial endocarditis are emphasized because of the supposed rarity of this condition. In 18 of the 24 cases of auricular fibrillation, the diagnoses were based on electrocardiographic as well as clinical evidence. Electrocardiograms had been obtained in every case in which auricular fibrillation antedated the onset of bacterial endocarditis.

DISCUSSION

There are differences in the results of this study and of other reported studies in regard to the frequency of the coexistence of auricular fibrillation and bacterial endocarditis. The discrepancy is difficult to explain. This report is based upon the study of consecutive cases taken from the protocols of the three hospitals mentioned. In every instance there was a thorough study of both the pathologic protocols and the hospital charts, and the existence of bacterial endocarditis was confirmed by autopsy.

In comparison with the incidence of auricular fibrillation in rheumatic heart disease which is usually accepted (40 to 53 per cent in the studies of de la Chapelle, Graef, and Rottino,[8] DeGraff and Lingg,[9] and Stone and Feil[10]), the coincidence of auricular fibrillation and bacterial endocarditis is low. However, in the present study no basis has been found for postulating a protective mechanism on the part of auricular fibrillation against the development of bacterial endocarditis, nor does there seem to be anything to suggest that these two disorders are mutually exclusive. The answer to this problem seems to depend

upon two factors which contribute to the development of auricular fibrillation: the integrity of the myocardium and the duration of the disease affecting the heart.

Congestive heart failure may be taken to be an expression of an inefficient myocardial function. In the 196 cases of bacterial endocarditis, the incidence of congestive failure, as indicated by chronic passive congestion of the liver, was about 40 per cent. However, in the 24 cases with auricular fibrillation 91 per cent showed congestive failure, and in the 21 cases of persistent auricular fibrillation, congestive failure was present in every instance. In their study of rheumatic hearts, de la Chapelle, Graef, and Rottino[8] found that the incidence of congestive failure was 88 per cent. Thus, in the cases of bacterial endocarditis reported, the percentage incidence of congestive failure is somewhat less than half that found in chronic rheumatic heart disease.

In regard to the duration of rheumatic heart disease, it is accepted that the incidence of auricular fibrillation in heart disease increases with the age of the patients. DeGraff and Lingg,[9] investigating the course of rheumatic fever in adults, reported that auricular fibrillation "is a late manifestation in rheumatic heart disease." They further stated, "It appears, then, that patients who died of subacute bacterial endocarditis have not had rheumatic heart disease long enough to develop auricular fibrillation; hence, the rare coexistence of the two conditions." Garvin,[11] in a study of rheumatic heart disease, concluded that "in fatal rheumatic heart disease, as in fatal hypertension and coronary disease, auricular fibrillation is found in older patients, while a normal cardiac mechanism usually is encountered in younger patients." It was previously mentioned that the greatest number of deaths from bacterial endocarditis was encountered in the age group from 20 to 29 years, and that the general impression was that bacterial endocarditis is a disease of the younger age group. Rheumatic heart disease with congestive failure has its highest incidence in the fourth and fifth decades (Clawson[12]).

That the grade of mitral stenosis is a factor in determining the incidence of auricular fibrillation does not seem to be a conclusion justified by this study; for, as has been previously noted, the coincidence of auricular fibrillation and bacterial endocarditis was about the same whether the mitral valve was involved alone, whether the mitral and aortic valves were both involved, or whether only the aortic valve was involved. Our belief that auricular fibrillation does not depend upon the degree of mitral stenosis is in full agreement with the conclusions of de la Chapelle, Graef, and Rottino[8] and of Segal.[6] It seems much more probable that the pathogenesis of auricular fibrillation is more closely related to the myocardial integrity, both physiologic and anatomic, than to the degree of severity of mitral stenosis per se.

The most probable explanation of the fact that auricular fibrillation is present less frequently in bacterial endocarditis than in rheumatic heart disease without bacterial endocarditis is that sepsis intervenes to cause death before the patient with bacterial endocarditis develops auricular fibrillation and congestive failure indicative of severe myocardial failure.

CONCLUSIONS

1. In 286 patients with bacterial endocarditis, 36 examples (12.59 per cent) of auricular fibrillation were encountered.

2. Of the 196 cases in which the character of the fibrillation was analyzed, three were of the paroxysmal type and 21 were of the persistent variety. Of these 21 cases of persistent fibrillation five definitely had an antecedent bacterial endocarditis, in six the auricular fibrillation was definitely present before the onset of bacterial endocarditis, and in 10 both processes were present when our observations began.

3. The incidence of auricular fibrillation was approximately the same irrespective of the type of valvular involvement.

4. The reason that the incidence of auricular fibrillation is significantly lower in bacterial endocarditis than in rheumatic heart disease seems to be that in most cases of bacterial endocarditis fatal sepsis intervenes while the patients are relatively young and before the disturbance of the myocardial integrity becomes severe.

5. The results of this study suggest that the coexistence of auricular fibrillation and bacterial endocarditis is not so rare as was previously supposed, and that one should therefore be cautious in using this point as a diagnostic aid.

REFERENCES

1. Blumer, G.: Subacute Bacterial Endocarditis, Medicine 2: 105, 1923.
2. Thayer, William S.: Studies on Bacterial (Infective) Endocarditis, Bull. Johns Hopkins Hosp. 22: 1, 1926.
3. Rothschild, M. A., Sacks, B., and Libman, E.: Disturbances of Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, AM. HEART J. 2: 356, 1927.
4. Fulton, M. N., and Levine, S. A.: Subacute Bacterial Endocarditis With Special Reference to Valvular Lesions and Previous History, Am. J. M. Sc. 183: 60, 1932.
5. Laws, C. L., and Levine, S. A.: Clinical Notes on Rheumatic Heart Disease With Special Reference to Cause of Death, Am. J. M. Sc. 186: 833, 1933.
6. Segal, M. S.: Auricular Fibrillation and Auricular Flutter in Course of Subacute Bacterial Endocarditis; Report of a Series of Cases, New England J. Med. 212: 1077, 1935.
7. Christian, Henry A.: Determinative Background of Subacute Bacterial Endocarditis, Am. J. M. Sc. 201: 34, 1941.
8. de la Chapelle, C. E., Graef, I., and Rottino, A.: Studies in Rheumatic Heart Disease; Analysis of 119 Hearts With Special Reference to Relationship of Auricular Fibrillation to Mitral Valvular Deformity and Certain Rheumatic Tissue Changes, AM. HEART J. 10: 62, 1934.
9. DeGraff, A. C., and Lingg, C.: Course of Rheumatic Heart Disease in Adults; Influence of Type of Valvular Lesion on Course of Rheumatic Heart Disease, AM. HEART J. 10: 478, 1935.
10. Stone, C. S., and Feil, H. S.: Mitral Stenosis; Clinical and Pathological Study of 100 Cases, AM. HEART J. 9: 53, 1933.
11. Garvin, Curtis E.: Age, Sex and Race Relationships of Auricular Fibrillation, Am. J. M. Sc. 203: 788, 1942.
12. Clawson, B. J.: Diseases of the Heart, in Bell's Textbook of Pathology, ed. 5, Philadelphia, 1944, Lea & Febiger, p. 564.

PATHOLOGIC STUDY OF THIRTY-ONE CASES OF SCRUB TYPHUS FEVER WITH ESPECIAL REFERENCE TO THE CARDIOVASCULAR SYSTEM

LIEUTENANT COLONEL HAROLD D. LEVINE, M.C.
ARMY OF THE UNITED STATES

SINCE the early phases of the Papuan campaign scrub typhus fever has been recognized as an important problem of military medicine in the Southwest Pacific theater of operations.[1-3] Experience with the disease has caused particular concern for the real or hypothetical cardiac complications of the disease. Some support was lent to this attitude by the histopathologic studies of Kouwenaar,[4] Kouwenaar and Wolff,[5] and Corbett[6] and the clinical studies of Lipman, Byron, and Casey.[7] Other studies, on the contrary, pointed out the possibility of misinterpreting certain physical findings as the result of heart disease[8] and failed to establish evidence for the existence of chronic heart disease as a sequel of the disease.[9, 10] From his study of an epidemic of 230 cases in one of the islands of the Southwest Pacific in early 1944, Logue[11] stated that "the probability of permanent myocardial damage should be given further consideration." This conclusion was unfortunately misquoted in a popular newsmagazine which stated that "he suspects that all have permanent heart damage." Personal interviews with many medical officers throughout this area have shown that this bogey still persists. It seemed worth while, therefore, to examine a representative sample of pathologic material, focusing attention upon any abnormalities of the cardiovascular system.

METHODS AND MATERIAL

The material for this study comprises the gross and microscopic findings of thirty-one cases of scrub typhus fever autopsied at the Third Medical Laboratory during the year 1944 and made available to me through the courtesy of Captain George P. Smith. The cases included in the study have not been previously reported. The patients ranged in age from 19 to 44 years with a mean age of 24 years (see Table I). Death occurred in from six to twenty-four days after the onset of the disease. The mean duration of the illness was thirteen days. More than half of the deaths occurred between the twelfth and fifteenth days.

Excepting the data substantiating the clinical diagnosis, practically all of the material of this study was derived from the gross autopsy findings and microscopic examination of the tissues. In all thirty-one cases the diagnosis of scrub typhus fever was well established. Every record described regional and generalized lymphadenopathy and a rash, and all but one described a characteristic eschar. The patients' sera agglutinated the OX-Kingsbury strain of the *proteus* bacillus in significant titer in nineteen cases, and in nine cases the

Received for publication June 5, 1945.

OX-K agglutination could not be carried out. Table I is a consolidation of much of the essential data of this study. The severity of the changes is graded as follows: + = mild, ++ = moderate, +++ = severe, and ++++ = very severe.

PATHOLOGIC CHANGES IN THE HEART AND OTHER ORGANS

I. The Heart.—The hearts ranged in weight from 260 to 500 grams; the mean weight was 330 grams. In four cases the consistency was firm and the color was rusty red or dark mahogany brown. In 27 cases the heart was pale, soft, flabby, or slightly friable. Although two hearts contained small atheromatous plaques in the proximal portions of the coronary arteries, in all cases these vessels were widely patent throughout. In every instance the valves were free, delicate, and competent, and the measurements of the valve rings were normal. In 22 cases there were subepicardial petechial hemorrhages, and in two cases there were subendocardial petechial hemorrhages. In only one case was there a macroscopic hemorrhage into the heart muscle proper.

In six cases the microscopic appearance of the heart was perfectly normal and compact; in twenty-five, microscopic changes were observed. These were located principally in the myocardium, but in 16 cases there were also epicardial or endocardial changes. In five cases the myocardium seemed loose, frayed, and lacy, the muscle fibers being separated either by a thin fibrin network or an inflammatory exudate. This consisted of lymphocytes, plasma cells, and large mononuclear cells, some of which had eosinophilic cytoplasm and somewhat vesicular nuclei usually containing nucleoli. In a few cases there was also a sprinkling of polymorphonuclear leucocytes. This type of exudate was distributed diffusely in the endomysial spaces in four cases and as a cuff around blood vessels in seven; in 14 cases there were both a perivascular and an interstitial distribution. As Table I shows, the degree of this reaction was slight in 11 instances, moderate in six, severe in four, and very severe in four. In 13 cases there was a slight to moderate exudation of similar cells into the endocardium which might be slightly thickened, and in 16 cases the cells were found in the fibrous or fatty tissue of the epicardium. Fig. 1 shows an example of this type of reaction. In both locations the reaction was generally continuous with an identical reaction in the contiguous myocardium, but in a few instances the epicardial exudate was perivascular in distribution.

Of the twenty-five cases showing carditis, thirteen showed intact heart muscle fibers throughout with normal nuclear and cytoplasmic structure, but in twelve cases the cytoplasm had undergone minor degrees of hyaline degeneration, loss or indistinctness of striation, vacuolization of the cytoplasm, or fragmentation of the muscle fibers. Usually this muscle fiber necrosis was restricted to the cytoplasm but in two cases nuclear degeneration was also observed. An extreme degree of this type of myocardial degeneration is illustrated in Fig. 2. In one part of the field an intact muscle fiber is seen, and on the opposite side a fiber shows hyaline degeneration, vacuolation, and fragmentation. The cytoplasmic changes, when present, were most pronounced in the regions of focal exudation. In two cases this reaction involved the subendocardial layers of the

TABLE I. CARDITIS, PNEUMONIA, AND CONGESTIVE FAILURE IN SCRUB TYPHUS FEVER

CASE	AGE (YRS.)	DURATION IN DAYS	HEART		LUNGS				LIVER		KIDNEYS			ASCITIC FLUID (C.C.)	EDEMA	PLEURAL FLUID RIGHT (C.C.)	PLEURAL FLUID LEFT (C.C.)	PERICORDIAL FLUID (C.C.)
			WEIGHT GM.	CARDITIS	WEIGHT (GM.) RIGHT	WEIGHT (GM.) LEFT	PNEUMONIA	CONGESTION	WEIGHT GM.	CONGESTION	WEIGHT (GM.) RIGHT	WEIGHT (GM.) LEFT	CONGESTION					
1	–	16	395	++++	1,130	960	+	+++	2,680	+	230	–	0	500	0	0	200	100
2	22	12	500	++++	950	900	+++	++	1,900	+	285	290	+	0	0	1,500	1,500	300
3	24	12	380	++++	850	775	+++	+++	2,630	++	235	225	++	500	0	0	0	50
4	37	24	270	++++	1,300	1,200	++++	++	1,900	0	220	220	0	0	0	0	0	0
5	36	15	350	+++	1,250	1,050	+++	++	1,950	0	290	265	0	0	0	0	0	0
6	30	14	370	+++	1,215	1,100	+++	++	2,026	0	240	225	0	0	0	0	0	30
7	30	15	330	+++	1,000	885	+++	++	1,880	+	200	235	++	0	+	0	0	30
8	22	16	275	+++	1,200	900	+++	++	1,800	0	150	150	+	0	0	0	0	0
9	30	18	450	++	1,400	–	++	++	1,800	++	300	200	+++	700	++	1,500	1,500	200
10	23	13	270	++	1,030	910	+++	++	2,050	+	225	245	++	0	0	0	400	50
11	22	17	260	++	800	650	++	+	–	0	265	245	+	0	0	0	0	0
12	44	7	310	++	1,400	1,150	++++	++	2,200	+	170	170	+	0	0	0	0	0
13	21	15	415	++	735	910	+++	++	2,230	++++	250	300	++	300	++	400	400	150
14	43	13	340	++	700	700	++	+	2,000	0	245	285	0	0	0	0	0	0
15	32	–	325	+	1,100	950	+++	+++	2,100	0	210	190	++	0	0	0	0	0
16	20	20	405	+	545	545	+	+	2,200	+	225	290	+++	0	++	0	0	25
17	19	10	300	+	900	850	++	++	1,850	0	–	–	+++	500	0	250	250	60
18	–	14	290	+	1,200	1,100	++	++	2,500	0	260	260	0	75	0	0	0	75
19	27	12	315	+	1,180	–	+++	++	1,700	++	190	190	+++	0	+	0	0	50
20	24	9	315	+	950	750	+++	+++	2,075	++	240	250	++	200	0	500	500	–
21	22	8	335	+	1,265	1,065	0	+	1,950	++	185	230	++	0	0	0	0	50
22	25	9	390	+	1,200	950	++	++	1,900	+	210	190	++	500	0	500	500	100
23	22	12	360	+	1,260	1,230	++	++	2,290	++	180	200	+	700	+	600	600	30
24	–	14	380	+	790	745	++	++	2,410	++	230	230	+++	800	+	1,000	1,000	100
25	–	–	300	+	750	750	+++	++	2,400	+++	–	–	++	100	0	250	250	–
26	–	12	290	0	900	850	+++	++	1,850	0	190	200	0	1,500	0	50	50	0
27	22	13	275	±	1,300	700	++++	++	2,350	0	210	190	0	250	0	250	0	0
28	27	10	355	0	955	885	+++	+++	1,910	0	200	180	+	100	0	0	0	0
29	21	6	280	0	500	450	+	0	2,000	+	225	250	+	0	+	0	0	30
30	–	12	280	0	690	670	++	++	2,300	0	190	190	++	0	0	0	0	50
31	26	14	275	0	600	550	++	0	2,300	++	–	–	0	0	0	0	0	0

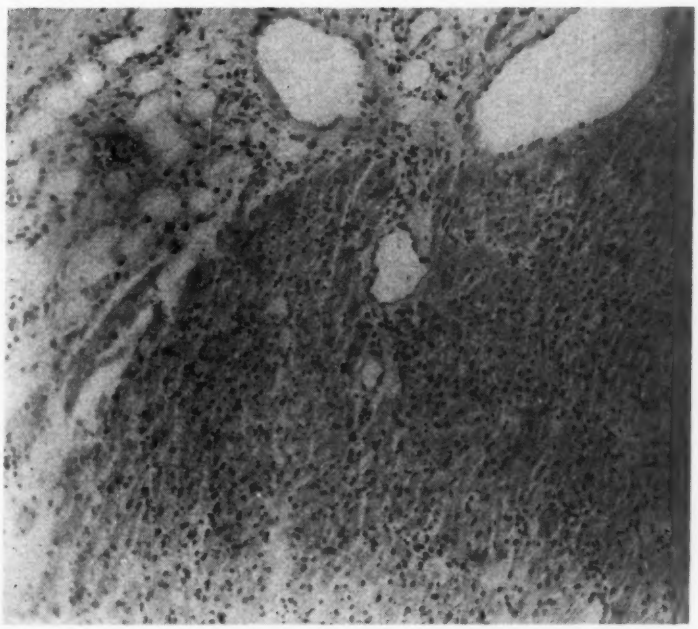


Fig. 1.—Case 9. Pericardial infiltration in scrub typhus fever. (×20.) For their courtesy and cooperation the author is indebted to Colonel Dwight M. Kuhns and Sergeant Dave Brunk of the Nineteenth Medical General Laboratory where the photomicrographs illustrated in this article were made.

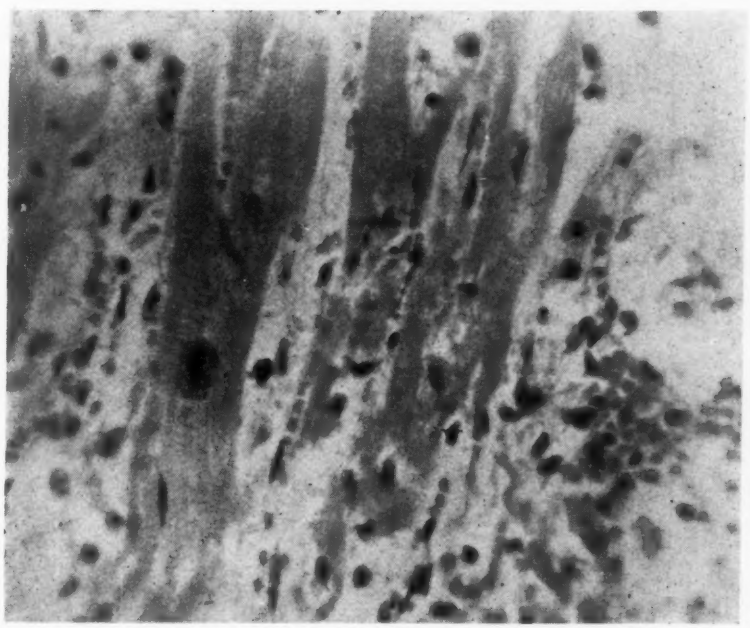


Fig. 2.—Case 2. Myocardial necrosis in scrub typhus. Note the relatively intact muscle fiber on the left in contrast to the fibers on the right which show hyaline degeneration, vacuolation, and dissolution. (×950.)

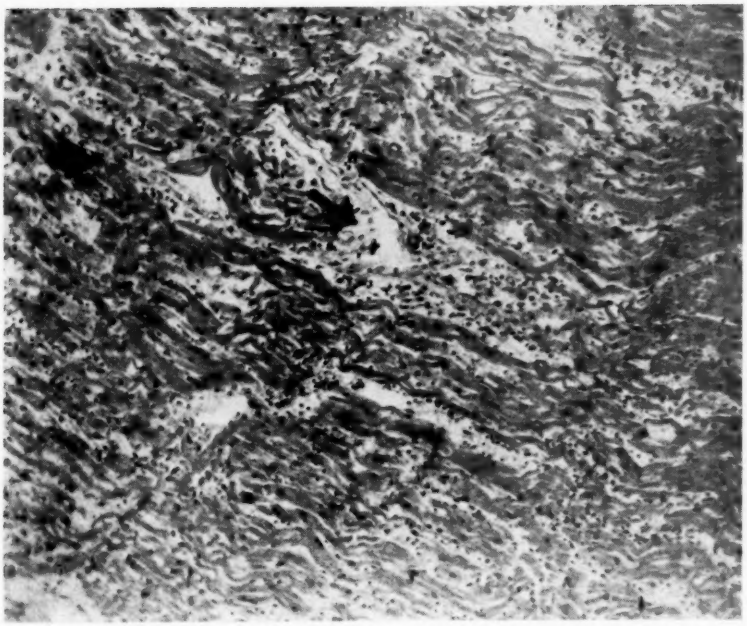


Fig. 3.—Case 8. Endothelial proliferation in one of the smaller vessels of the heart. Note the focal perivascular infiltration. Arrow indicates an area of heaping up of the endothelial cells. (×20.)

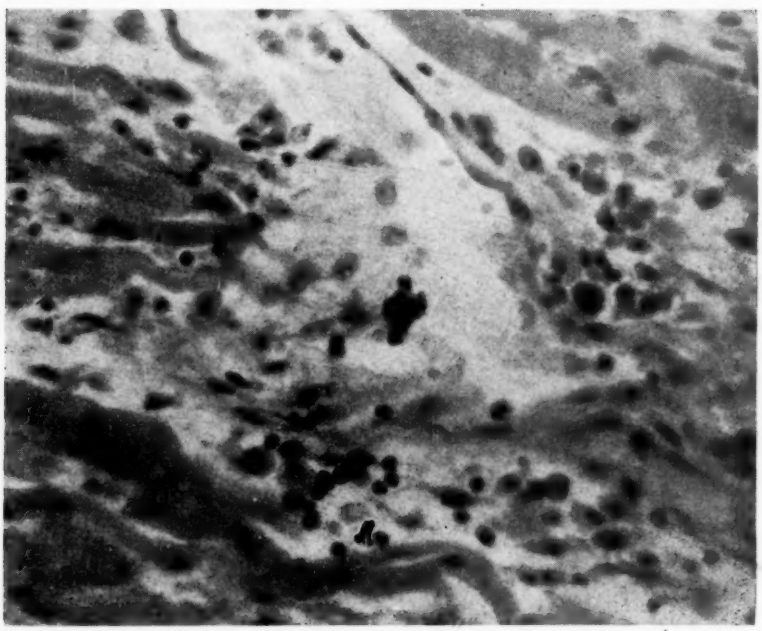


Fig. 4.—Case 8. Same section under higher magnification. Shows endothelial hyperplasia more clearly. (×440.)

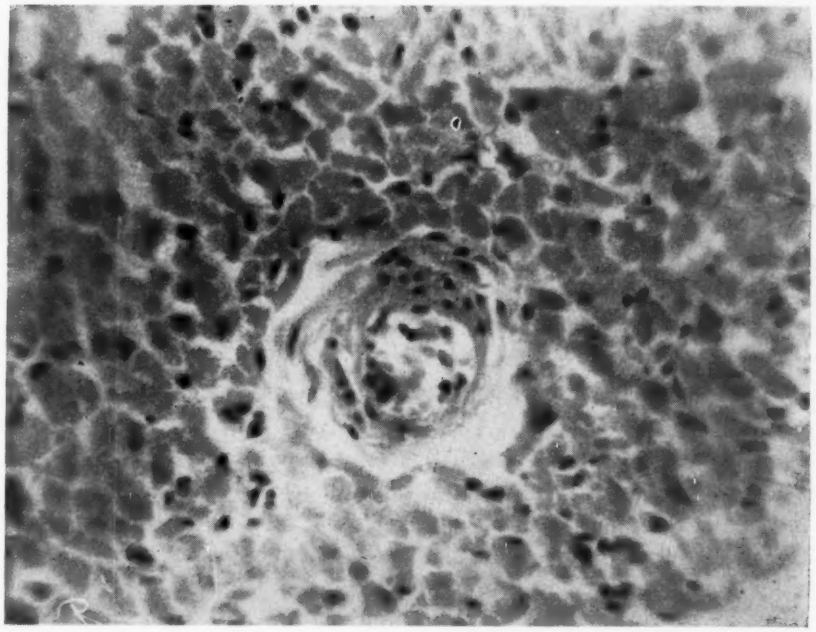


Fig. 5.—Case 14. Eccentric endothelial hyperplasia in a larger blood vessel in one of the papillary muscles of the left ventricle. (×440.)

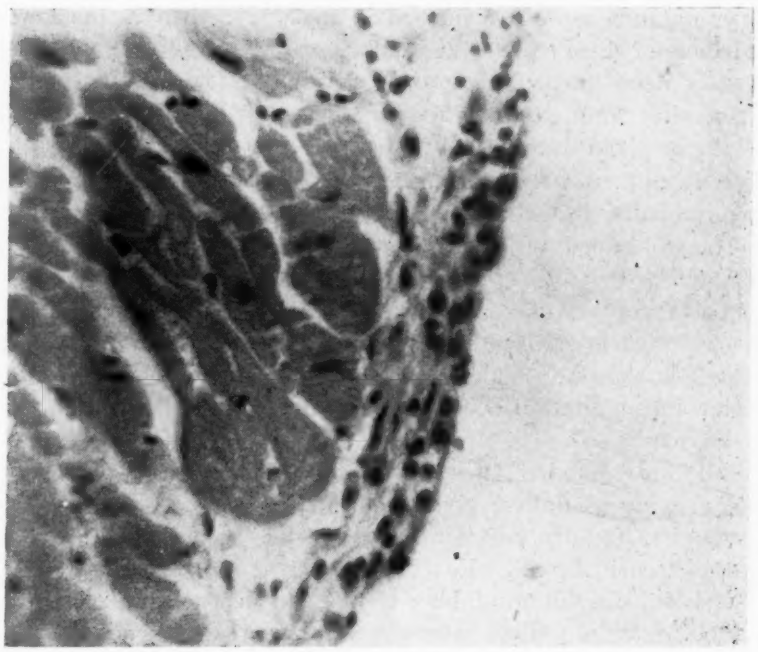


Fig. 6.—Case 3. Endocardial hyperplasia in the left ventricle. Whereas this layer should consist of a flat ribbon of spindle-shaped endothelial cells, the cells are heaped up and almost cuboidal in shape. (×440.)

myocardium. Though a planned systematic investigation of the conducting tissues of the heart was not made, inflammatory reactions of slight degree were observed in the Purkinje tissue of the papillary muscles in two cases. Evidence of fibrous tissue replacement of muscle fibers could not be established clearly.

The endothelium of the smaller blood vessels in the regions of focal perivascular exudation often showed proliferative changes (see Figs. 3, 4, and 5). Such piling up of the endothelium was noted in nine cases. No definite endothelial necroses could be demonstrated. Similar proliferative endovascular changes were not observed in the larger coronary vessels or in the intermediate-sized vessels lying in the fibrous tissue septa of the myocardium. In six cases the endothelium of the left ventricle was thickened by a similar mild endothelial hyperplasia (see Fig. 6).

II. The Lungs.—Except in seven instances in which there were old pleural adhesions and in three cases in which there were recent fibrinous adhesions on the lateral or diaphragmatic surfaces of one or both lower lobes, the pleural surfaces of both lungs were smooth, free, and glistening, showing, in seven cases, a varying number of subpleural hemorrhages. The right lungs varied in weight from 500 to 1,400 grams, the mean weight being 1,000 grams. The corresponding weights for the left lungs were 450, 1,230, and 885 grams, respectively. In most instances the lower lobe of each lung was either uniformly or spottily solid in consistency, lacking normal crepitation. In two cases, in addition to the involvement of the lower lobes, there was similar solidification of the middle lobe of the right lung and in two cases, of an upper lobe as well. In only two cases was the consolidation more pronounced in the upper than in the lower lobes. The cut surfaces of these more solid portions of the lungs were moist and either homogeneously deep purple or mottled, showing differences in color ranging from salmon pink through rusty red to plum purple. On scraping, the cut surface of the involved lung tissue exuded a frothy pink or red material.

In three cases there were small, hard, sharply demarcated grayish red raised areas, roughly lobular in distribution which appeared to be pulmonary infarcts. The protocols contained no description of the dissection of the pulmonary arteries or veins.

With one exception every case in this series showed some degree of inflammatory reaction in the lungs on microscopic examination. The severity of those changes is shown in Table I. The inflammatory reaction consisted of intra-alveolar and interstitial exudation of lymphocytes, plasma cells, and large mononuclear cells.

In seven cases in which the illness was of more than average duration there was a varying admixture of polymorphonuclear leucocytes in the exudate. This reaction was usually heaviest in the region of bronchioles and in such instances the bronchioles likewise contained a suppurative type of exudate. Fibrin deposition, dissolution of lung tissue, and degenerated cocci were often noted in such areas. In three cases the exudate was predominantly polymorphonuclear. These changes were regarded as evidences of secondary bacterial infection.

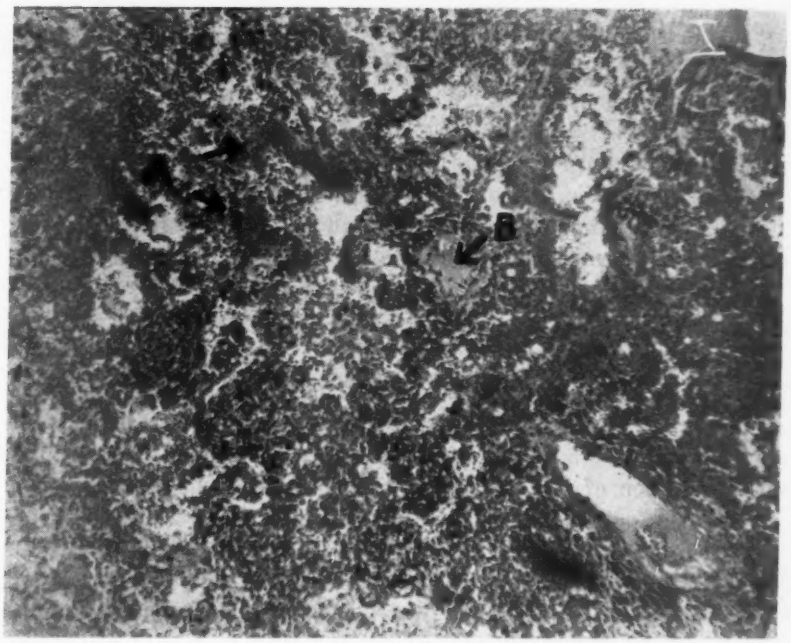


Fig. 7.—Case 13. Severe pneumonic infiltration showing mononuclear type of exudate, hyaline degeneration of alveolar epithelium (*A*) and the presence of "edema fluid" in some of alveoli (*B*). (×20.)

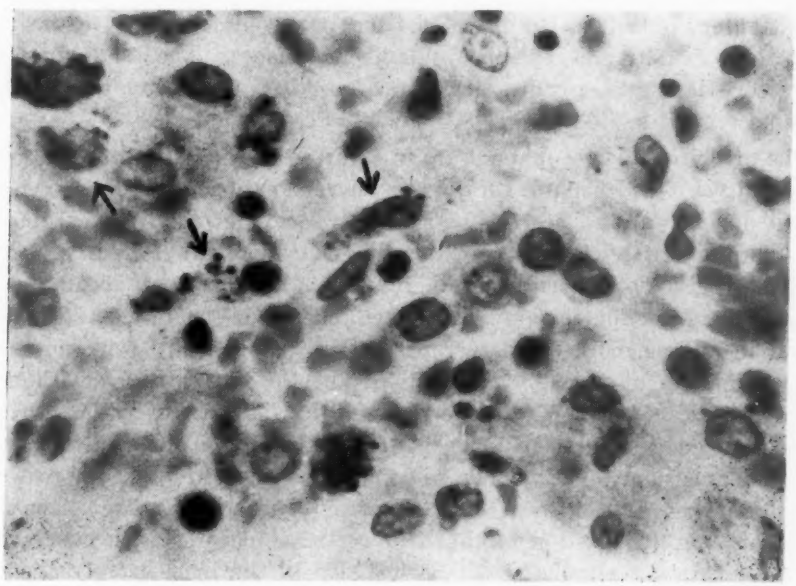


Fig. 8.—Case 22. Characteristic cellular exudate in lung. Note lymphocytes, plasma cells, mononuclear cells, extravasted erythrocytes, and "heart failure" cells, the latter indicated by arrows. (×950.)

The alveolar walls were well maintained in some cases but very indistinct in others. They often were completely ruptured and, in a few instances, were replaced by hyaline, (see Fig. 7). Marked atelectasis was noted in some portions of the lungs in most cases. The blood vessels of the supporting tissue of the lung and of the alveolar walls were moderately to markedly congested and were surrounded by mild to moderate round cell infiltration. In heavily congested areas large numbers of erythrocytes had broken into the alveolar spaces; occasionally they filled many continguous alveoli. In regions of hemorrhage many large mononuclear cells, much larger than those already described as part of the cellular exudate and containing granules of golden pigment material, were observed in the alveoli. These would correspond to the "heart failure cells" of the older pathology (see Fig. 8).

In regions adjacent to areas showing moderate or heavy inflammation, the exudate was thinner and a pale pink homogenous material filled the alveoli in whole or part. This was interpreted as "edema fluid." The combination of hyaline degeneration of the alveolar epithelium, hemorrhagic edema, and mononuclear exudation gave an appearance reminiscent of that observed in the pandemic of influenza in 1918. In none of the blood vessels of the lung were ante-mortem thrombi seen.

III. The Liver.—In eight cases in this series the liver extended below the right costal margin from 2 to 8 cm., as measured in the midclavicular line. The liver edge was described as rounded in nine cases and sharp in the remaining twenty-two cases. The organs varied from 1,700 to 2,680 grams in weight, the mean weight in the series being 2,050 grams. The surface was always smooth and glistening, but it varied in color from pale yellow (rare) to dark brown and, in three cases, it showed subcapsular hemorrhages. The cut surface showed a characteristic "nutmeg" appearance in four cases and "engorgement" in an additional six cases.

The principal microscopic picture in eighteen cases was that of congestion of the central veins and hepatic sinusoids with vacuolation, granular degeneration, pigment deposition, and necrosis of the central cells of the hepatic lobules. In the remaining thirteen cases there was no congestion. In four of the eighteen cases showing hepatic congestion there was no evidence of accumulations of fluid elsewhere; in the remaining fourteen, edema of the feet or accumulations of fluid in one or more of the serous cavities of the body were noted. Conversely, eighteen of the nineteen patients in the entire series with anasarca showed hepatic congestion of some degree. In fourteen of the eighteen cases with hepatic congestion there was some degree of myocarditis; in the remaining four there was none. Conversely, of twentyfive cases in which there was some degree of myocarditis, fifteen showed hepatic congestion and ten showed none. Hence, although congestion of the liver occurred parallel with congestion elsewhere, carditis was associated with congestion of the liver in only about three-fifths of the cases.

In twenty-eight cases there was some increase in the cellular infiltration of the periportal spaces. The cells in this region were of the same type as those

described in the heart and comprised lymphocytes, plasma cells, and mononuclear cells. In fourteen cases the cellular infiltration was associated with some degree of peripheral necrosis. In six cases there was noted a focal type of necrosis, of irregular distribution, with a light to moderate focal inflammatory reaction of the same cellular type as that described previously. In several cases there were various degrees of congestion, periportal inflammation, and central, peripheral, or focal necrosis in the same individual.

IV. The Kidneys.—The gross appearance of the kidneys was not remarkable. They varied in weight from 180 to 300 grams, the mean weight being 225 grams. In seventeen cases the cut surface of the kidneys was normal pink. In seven it was pale pink and in seven deep purplish red. In seven there were hemorrhages into the mucosa of the renal pelvis. One kidney showed several small subcapsular hemorrhages and a few hemorrhagic areas in the cortex.

In twenty-two cases the principal microscopic feature was congestion of the renal blood vessels with erythrocytes, which appeared most marked in the pyramidal portion but occasionally was seen in the glomeruli as well. In nine of the thirty-one cases studied there was no congestion. As with the liver, there was a high degree of correlation between renal congestion and the presence of myocarditis, and usually, renal congestion occurred parallel with hepatic congestion. Viewed from the other angle, nineteen of the twenty-five cases in the series showing myocarditis had an associated renal congestion whereas six had none.

Multiple small hemorrhages were noted among the straight tubules in sixteen cases and in Bowman's capsule in one. In fifteen cases there was an inflammatory exudate in the renal parenchyma, usually in the medulla, consisting of lymphocytes, plasma cells, and mononuclear cells. In about half of these cases the interstitial exudate was diffuse. In the other half the exudate was focal in distribution and associated with focal necrosis of the regional tubular epithelial cells. Post-mortem autolysis of varying degrees was noted in the tubules in twenty cases.

V. The Suprarenal Glands.—Excepting small hemorrhages in the fascial tissues surrounding the gland (in two cases) or into the adrenal parenchyma (in two cases) and a deep red discoloration of the medulla (in six cases) the gross appearance of the external and cut sections of the suprarenal glands was quite normal. In thirteen cases vascular congestion was noted. This was most prominent in the medulla but extended variable distances into the adrenal cords. Extravasation of blood into the adrenal cortex was seen in a few cases (Fig. 9). Focal necroses and inflammatory reactions of the same type as those described in other organs were seen in six cases, occasionally medullary but usually cortical in location (Fig. 10).

Congestive, hemorrhagic, and inflammatory changes, therefore, were not as frequently observed in the suprarenal glands as in the kidneys. But, with two exceptions, when present they were associated with some degree of carditis.

VI. The Brain and Meninges.—Although minor cerebral changes occurred in the majority of cases in only ten were they considered extensive or severe enough to be important. In two cases the cerebral convolutions were described

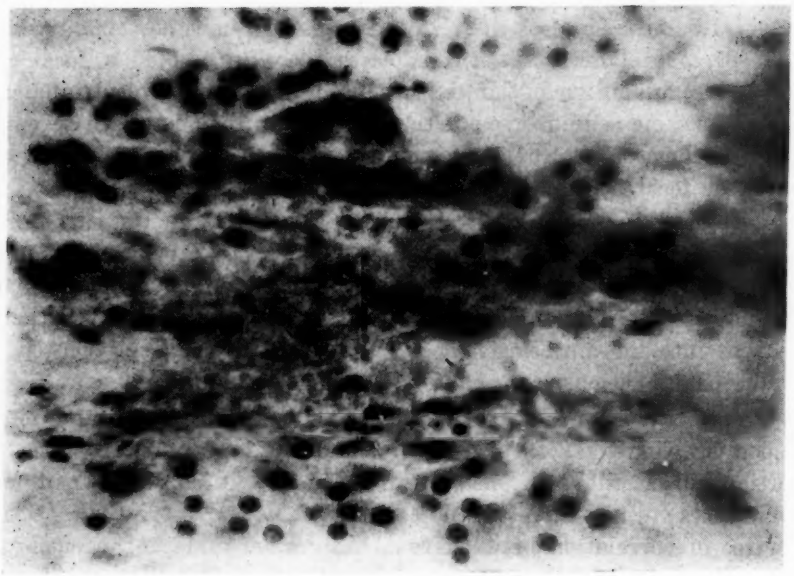


Fig. 9.—Case 3. Hemorrhage in adrenal cortex. (×440.)

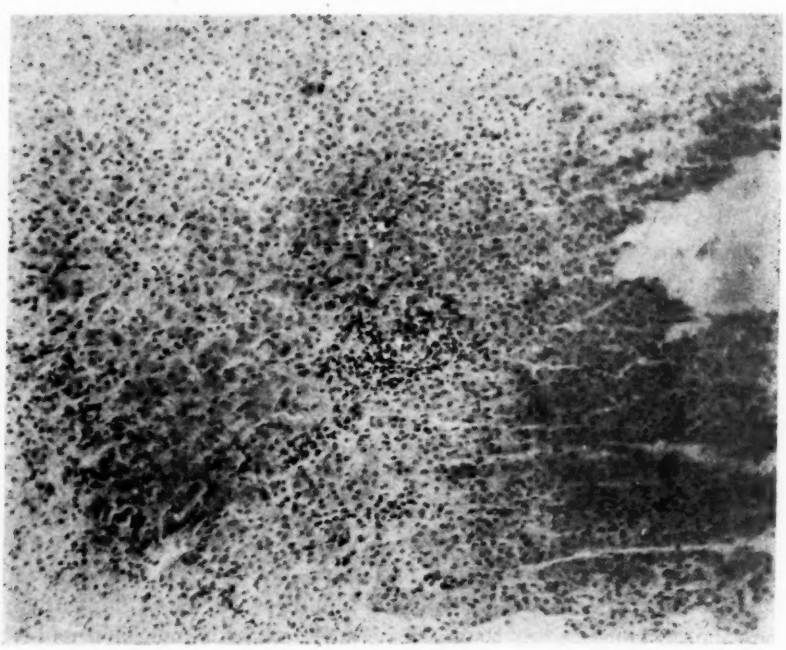


Fig. 10.—Case 1. Focal necrosis and infiltration in adrenal cortex. (×20.)

as flattened. The leptomeninges were congested in eight cases. In eleven cases petechial hemorrhages were seen with the naked eye on the cut surface of the brain.

A surprising microscopic feature was the infiltration noted in the meninges. These contained a diffuse (in 12 cases) or focal (in three cases) large and small mononuclear cell exudate. In fourteen cases there were focal lesions consisting either of a perivascular lymphocytic and mononuclear cell exudate or dense clusters of microglial cells (the so-called "typhus nodules"). In eleven cases these nodules were more or less uniformly distributed throughout the brain substance and in three only in certain regions of the brain. In eight cases microscopic hemorrhages were observed in the brain substance. Thromboses were never encountered.

CONGESTIVE HEART FAILURE

Edema of the ankles or accumulations of fluid in at least one of the serous spaces of the body was noted in twenty-three cases in this series. All but two of these were associated with some degree of carditis. In all cases the anasarca was associated with visceral congestion. On the contrary, of 25 cases showing carditis, 18 showed some anasarca while seven did not. Ascitic fluid, noted in 14 cases, varied in volme from 50 to 1,500 c.c., the mean being 500 cubic centimeters. Hydropericardium was noted in 13 cases, the pericardial fluid was estimated at between 50 and 300 c.c., mean volume being 75 cubic centimeters. Eleven cases showed right, and twelve left, hydrothorax. The volume of pleural fluid varied from 50 to 1,500 c.c. with a mean of 500 cubic centimeters. Edema of the feet or ankles was noted in eight cases.

HEMORRHAGIC PHENOMENA IN SCRUB TYPHUS

A notable feature in the present series was the frequency of hemorrhagic manifestations. Subcapsular hemorrhage of the liver, subcapsular, parenchymatous, or submucous hemorrhage of the kidney, hemorrhage into the pleural and pericardial membranes, and hemorrhage into the suprarenal gland, lung, and brain have already been described. Hemorrhages were also observed in the mucosa of the gastrointestinal tract in ten cases. These were usually located in the upper portion, but in two cases the colon was involved as well. One of these patients passed gross blood in his stools. One patient had a severe hemoptysis; microscopic examination in this case showed large hemorrhages into the pulmonary alveoli. Seven patients had epistaxes; in three of these the bleeding was severe enough to require packing of the nose. One patient had a hemorrhage into the submucosa of the urinary bladder. Five had hemorrhages into the sclerae. One of these patients who had several subconjunctival hemorrhages also had a large hemorrhage into the rectus muscle sheath.

In two cases petechiae were observed in the skin. In one of these the petechiae were generalized; in the other they were limited to the feet. In two cases there were large ecchymoses in the skin. In one of these the ecchymotic area was located below the left axilla; in the other there was an ecchymosis below the right axilla and another in the scrotum.

DISCUSSION

From this study it appears that the cardiac changes in this series of cases of scrub typhus fever were exceeded in frequency only by pulmonary changes. Cardiac involvement was more frequent than meningoencephalitic lesions. Although cardiac changes occur in the great majority of fatal cases, they are present in varying degrees of severity. And, finally, it is apparent that, in a considerable proportion of patients with carditis, congestive heart failure, hitherto only vaguely and unconvincingly alluded to in the available clinical literature, actually develops.

The changes described here are quite similar to those found in European (epidemic) typhus fever.[12] The detection of endothelial proliferation in this series confirms the findings of Corbett.[6] This lesion was obvious in the smaller and medium-sized vessels of the heart, but not in the larger coronary vessels. Similar proliferative changes were sought, but not found, in the adventitial vessels of the gut, in the vasa vasorum of the aorta, and in the afferent arterioles of the renal glomeruli. The endothelial hyperplasia is not unlike that which has been described in European typhus. But here the similarity ends, because neither endothelial necroses nor thromboses were observed in the present series. The incidence of pericardial or endocardial infiltration was rather unusual in this series. In none of Corbett's seven cases[6] was endocardial infiltration described and in only one was subepicardial infiltration found.

The existence of adrenal changes, previously denied[13, 14] or not mentioned, is of some interest. These glands obviously are involved to some extent in the general picture of visceral congestion. They also show the same hemorrhages and focal necroses that other organs show. The changes are similar to those found in other infections, such as diptheria, or in intoxications such as that produced as a result of the injection of diptheria toxin.[15] Massive adrenal hemorrhage was not seen in the present series, and it is doubtful that any of the fatalities are attributable to acute adrenal insufficiency. Whether or not the asthenia, tachycardia, hypotension, and effort intolerance seen as the most striking sequelae of scrub typhus fever are related to the observed changes in the adrenals seems questionable.

Although it is more than likely that alterations in the walls of the blood vessels are responsible for the bleeding phenomena, references have appeared in the literature[13, 17] to a "diminished coagulability of the blood" in the disease. The results of investigation of intrinsic changes in the clotting mechanism are awaited with interest.

THE QUESTION OF RESIDUAL CARDIAC DAMAGE

As in Corbett's group, variable degrees of damage to the myocardial fibers were found in the present series. Of twenty-five cases with myocarditis, twelve showed myocardial necrosis of some degree. When present it was heaviest in the neighborhood of focal perivascular exudates or in the subendocardium. Accumulating clinical[16] and anatomic evidence tends to show, however, that

these changes eventually disappear, leaving no trace of previous damage. Williams, Sinclair, and Jackson[9] found neither cellular infiltration nor evidence of early fibrotic changes in the hearts of three soldiers who died of complications four to six weeks after attacks of scrub typhus. A more recent autopsy[10] performed on a soldier who died on the thirty-fifth day of scrub typhus from a complication not directly related to the disease showed identifiable, but practically completely healed, myocardial lesions. The resulting scar tissue was regarded as so slight as to be unlikely to interfere with normal function. The following case of a patient personally observed is very instructive because of the long period following the attack of scrub typhus fever and the occurrence of cardiac symptoms in the interim.

REPORT OF CASE

CASE 32.—In May, 1944, a 22-year-old infantryman had a severe attack of scrub typhus fever, associated with an eschar, a rash, regional and generalized lymphadenopathy, and a strongly positive OX-K agglutination reaction. The disease ran a two weeks' course with deafness, delirium, cough, cyanosis, signs of pneumonia, tachycardia, and hypotension. He was so sick that his name was placed on the seriously ill list. Following recovery he complained persistently of breathlessness and tachycardia on exertion, palpitation, precordial oppression, weakness, and exhaustion. These symptoms continued until November, 1944, when the patient developed severe acute infectious hepatitis which progressed to fatal acute yellow atrophy of the liver. Post-mortem examination showed a perfectly normal heart without infiltration or scarring.

Similar observations have been made following European typhus,[12] in which the heart is involved as severely and extensively as in scrub typhus, and also following diphtheria in which there is much more severe and extensive myocardial necrosis. There has been no question of chronic heart disease following either of these diseases. From the available evidence it is likely, therefore, that patients who survive scrub typhus fever ultimately show no residual cardiac damage.

SUMMARY AND CONCLUSIONS

1. Post-mortem studies carried out in thirty-one cases of scrub typhus fever showed pulmonary lesions in all but one case and cardiac lesions in twenty-five. Meningoencephalitic lesions were third in order of frequency.

2. The essential pathologic response to the infection consisted of endothelial proliferation and perivascular lymphocytic, plasma cell, and mononuclear cell infiltration.

3. The principal cardiac changes were in the myocardium, but the endocardium and pericardium frequently contained cellular exudates. These were lesions occurring in patients who succumbed to the disease during the acute phase and their presence lends no support to the hypothesis that myocardial damage persists in patients who have recovered from the disease. Necrosis of heart muscle fibers was observed in about half of the cases showing carditis. This was rarely severe.

4. The pathologic changes in various organs represent the composite effect of at least three possible factors: (a) The disturbance of blood supply pro-

duced by vascular injury and occasionally manifested by focal necrosis and hemorrhage, (b) the back-pressure effects from congestive heart failure, and (c) inflammatory changes.

5. Hemorrhagic phenomena were frequently observed. They were probably due to vascular injury. Petechial hemorrhages or ecchymoses occasionally were found in the skin.

6. Evidence does not point to residual cardiac damage in scrub typhus.

REFERENCES

1. Ahlm, C. E., and Lipshutz, J.: Tsutsugamushi Fever in the Southwest Pacific Theater, J. A. M. A. 124: 1095, 1944.
2. United States of America Typhus Commission: Scrub Typhus, Bull. U. S. Army M. Dept., No. 76, 52, (May) 1944.
3. Farner, D. S., and Katsampes, C. P.: Tsutsugamushi Disease, U. S. Nav. M. Bull. 43: 800, 1944.
4. Kouwenaar, W.: Investigations on Rickettsial Diseases in Sumatra; Pathologic Anatomy of Human Mite Fever, Geneesk. tijdschr. v. Nederl.-Indië 80: 1119, 1940.
5. Kouwenaar, W., and Wolff, J. W.: Rickettsia Infections in Sumatra, Proc. 6th Cong. Pac. Sc. Assoc. 5: 633, 1942.
6. Corbett, A. J.: Scrub Typhus, Bull. U. S. Army M. Dept., No. 70, 34 (November), 1943.
7. Lipman, B. L., Byron, R. A., and Casey, A. V.: Clinical Survey of Scrub Typhus Fever, Bull. U. S. Army M. Dept., No. 72, 63 (January), 1944.
8. War Dept. Technical Bulletin. (TB MED 31) Scrub Typhus Fever (Tsutsugamushi Disease), April 11, 1944.
9. Williams, S. W., Sinclair, A. J. M., and Jackson, A. V.: Mite-Borne (Scrub) Typhus in Papua and Mandated Territory of New Guinea. Report of 626 Cases, M. J. Australia 2: 525, 1944.
10. Scrub Typhus Not a Cause of Chronic Heart Disease, Bull. U. S. Army M. Dept., No. 84, 21 (January), 1945.
11. Logue, J. B.: Scrub Typhus. Report of Epidemic in Southwest Pacific, U. S. Nav. M. Bull. 43: 645, 1944.
12. Herzog, E., and Rodriquez, H.: Die Beteiligung des Myocards beim Fleckfieber. (Myocarditis exanthematica), Beitr. z. path. Anat. u. z. allg. Path. 96: 431, 1935-36.
13. Kawamura, von R.: Die Tsutsugamushi-Krankheit, Jena, Germany, 1930, Gustav Fischer, vol. 8, part 2, p. 1387.
14. Lewthwaite, R.: The Pathology of Tropical Typhus (Rural Type) of the Federated Malay States, J. Path & Bact. 42: 23, 1936.
15. Boyd, W.: Pathology of Internal Diseases, ed. 3, Philadelphia, 1940, Lea & Febiger, pp. 466-467.
16. Levine, H. D.: The Cardiac Complications of Scrub Typhus (Tsutsugamushi) Fever: a Study of Their Persistency, War Med. (In press.)
17. Ogata, N.: Die Tsutsugamushi-Krankheit. "Rickettsia tsutsugamushi," Arch. f. Schiffs-u. Tropen-Hyg. 39: 491, 1935.

AN ANALYSIS OF THE TIME RELATIONSHIPS WITHIN THE CARDIAC CYCLE IN ELECTROCARDIOGRAMS OF NORMAL MEN

I. The Duration of the Q-T Interval and Its Relationship to the Cycle Length (R-R Interval)

Captain Isadore Schlamowitz, M.C.
Army of the United States

THE Q-T interval and its relationship to the length of the cardiac cycle has been of interest to many workers. This subject has been investigated to ascertain its value in detecting and measuring abnormalities in the physiologic state of the cardiac conducting system as well as organic changes in the heart muscle itself. As research progressed, various facts concerning the relationship of the Q-T interval to the cycle length revealed themselves, and attempts were made to express this relationship in a number of ways. Lombard and Cope[1, 2] and Katz[5] studied this relationship after recording cardiac systole and cycle length by means of mechanical devices. The former authors expressed the relationship by means of the formula, Systole $= \frac{60}{K\sqrt{PR}}$, where K is a constant that varies with change in the subject's posture, and PR is the pulse rate per minute. This formula is the same as the more popular one suggested by Bazett[3] but is expressed differently. The latter, on the basis of a study of the electrocardiograms of 41 subjects, proposed the equation $Q\text{-}T = K\sqrt{C}$, where C is the R-R interval, or the cycle length, and K is a constant with the value 0.37 for men and 0.40 for women. Fenn[6] agreed that the square root formula expressed the relationship of Q-T and C in his ten cases, but he used 0.39 as the value of K. Fridericia[4] proposed the formula $Q\text{-}T = 8.22\sqrt[3]{C}$, as the one best expressing the relationship in his series of 50 cases. Since then other workers[7, 8, 10, 11, 13, 15, 23-29] have used either the square root formula, or the cube root formula, or both of these formulas in the study of various groups of patients in an attempt to determine a normal value for the constant K and the effect of various factors, including drugs and disease, upon it. A number of authors[9, 12, 16, 17, 20] found that the duration of the Q-T interval varied with the cycle length, but did not attempt to express this relationship in a formula. They did attempt to determine the effects of cardiac pathology and other factors on the length of Q-T. Adams,[14] after measuring the electrocardiograms of 50 men and 54 women and making a statistical analysis of these measurements, suggested that the Q-T and C relationship was linear rather than curvilinear as proposed by Bazett and Fridericia. His equations were: $Q\text{-}T = 0.1536\ (R\text{-}R) + 0.2462$, for men, and $Q\text{-}T = 0.1259\ (R\text{-}R) + 0.2789$, for women, and $Q\text{-}T = 0.1464\ (R\text{-}R) + 0.2572$ for the combined

Received for publication Aug. 14, 1945.

groups. Finally in 1939 and 1942, Ashman[19, 22] and Ashman and Hull[21] proposed the equation Q-T = K log [10(C + k)], where K is 0.375 for men and 0.385 for women, up to the age of 45 years; and k is 0.07 for all cases. This equation was offered as the one best expressing the Q-T and C relationship.

While attempting to apply one of the four equations, difficulty was encountered in reconciling the values arrived at with those found in the literature. Application of the other three equations also gave unsatisfactory results. It was then decided to investigate this subject, using a large group of normal individuals. The aim was to answer the following questions: (1) Is there a constant relationship between the Q-T interval and the cycle length (C)? (2) If there is such a relationship, or correlation, how predictable is it? (3) What kind of relationship is it, and how can it be expressed? (4) How great is the scatter? If it is great, this might explain the different values for the various constants, and the different equations already proposed. (5) What effect, if any, does physiologic tachycardia, e.g., the tachycardia occurring after exercise, have on the Q-T to C relationship? (6) How closely do the Q-T and C values predicted from the equations already proposed by the other workers agree with the data found in this study?

METHOD

Six hundred and fifty soldiers were observed for at least three days to determine whether or not organic disease was present. The body temperature, pulse rate, and respiratory rate were observed daily. A urinalysis was done in each case. A complete history was taken, and in the physical examination special emphasis was placed upon signs and symptoms of rheumatic fever, cardiac dysfunction, both organic and functional, circulatory disturbances, and diseases of all other types. Where there was any questionable finding, the subject was more completely studied and usually not included in this series.

The electrocardiograms were taken with an amplifier type of instrument, the General Electric Electrocardiograph, Model B, which was checked before beginning this study and periodically thereafter for accuracy of the timer and of the drum speed. The error was found to be –1.18 per cent and remained constant throughout. This error was taken into account in all measurements. Tracings were standardized so that a deflection of 1 cm. was equivalent to 1 millivolt.

In order to augment the number of short cardiac cycles, and to observe the effect of exercise on the relationship of Q-T to the cycle length, in each case a tracing was made at rest and immediately after exercise. An electrocardiogram consisting of the three standard limb leads was taken of each subject while he was sitting in a comfortable armchair, the beck rest of which was at an angle of 90 degrees to the seat. Then the subject hopped, so that his shoulders rose 6 inches at each hop, 100 times within sixty seconds. The exercise was done with the electrodes and lead wires in place. Immediately after exercise the patient resumed the sitting position and a tracing was taken on Lead II. When possible it was made long enough to record the return of the heart rate to approximately that of the resting state.

The criteria set forth by the American and New York Heart Associations were adhered to in reading and interpreting the electrocardiograms. In addition, any tracing showing a deviation of the electrical axis outside the range covered by the limits –15 degrees left and –105 degrees right was dropped from the series. A diphasic or inverted P_3 or T_3 was considered normal if it did not form part of a picture of myocardial damage. Where an irregular base line or any other artifact made the points from which the measurements were taken indistinct, the tracing was dropped from the series. The electrocardiograms were measured to the nearest 0.01 second with the aid of a four-power hand lens and a pair of especially fine needlepoint calipers. The cycle length was taken as the interval between the peaks of two consecutive R waves. The Q-T interval was measured from the beginning of the first deflection of the QRS complex to the end of the T wave. Lead II was used throughout, since it was found that the Q-T interval could be measured more accurately in this lead than in the other two leads. Furthermore, the length of the cycles and the Q-T intervals in the other leads did not exceed those found in Lead II. Cycles used for this study fulfilled the following requirement: Each cycle was one of a series of three or four consecutive cycles all of whose lengths, and the lengths of whose corresponding components, were identical. Only one cycle in each such group was used. In most cases more than one cycle was used both at rest and after exercise. It was felt that the cardiac conducting system was more or less equilibrated at each of the cycle lengths studied.

In Table I are listed the age distribution of the 495 cases retained for this study. The total number of cardiac cycles that were analyzed was 1,419, of which 790 were from tracings taken before exercise and 629 were from tracings taken after exercise.

To help minimize the discrepancies and variations that personal factors might introduce into a study of this kind, all the procedures except the urinalysis and the observations of temperature and respiratory rate were carried out by the author.

TABLE I. AGE DISTRIBUTION OF TOTAL NUMBER OF CASES

AGE (YRS.)	NO.	AGE (YRS.)	NO.	AGE (YRS.)	NO.
18	19	26	22	34	5
19	60	27	15	35	8
20	50	28	10	36	8
21	63	29	14	37	11
22	42	30	17	38	7
23	37	31	11	39	2
24	38	32	10	42	3
25	32	33	10	44	1
				Total	495

RESULTS AND DISCUSSION

To illustrate graphically the distribution of Q-T readings when plotted against the cycle length, a scatter diagram including all 1,419 readings was constructed (Fig. 1). There appears to be a definite and constant relationship between the two variables. How great this correlation is could not be determined

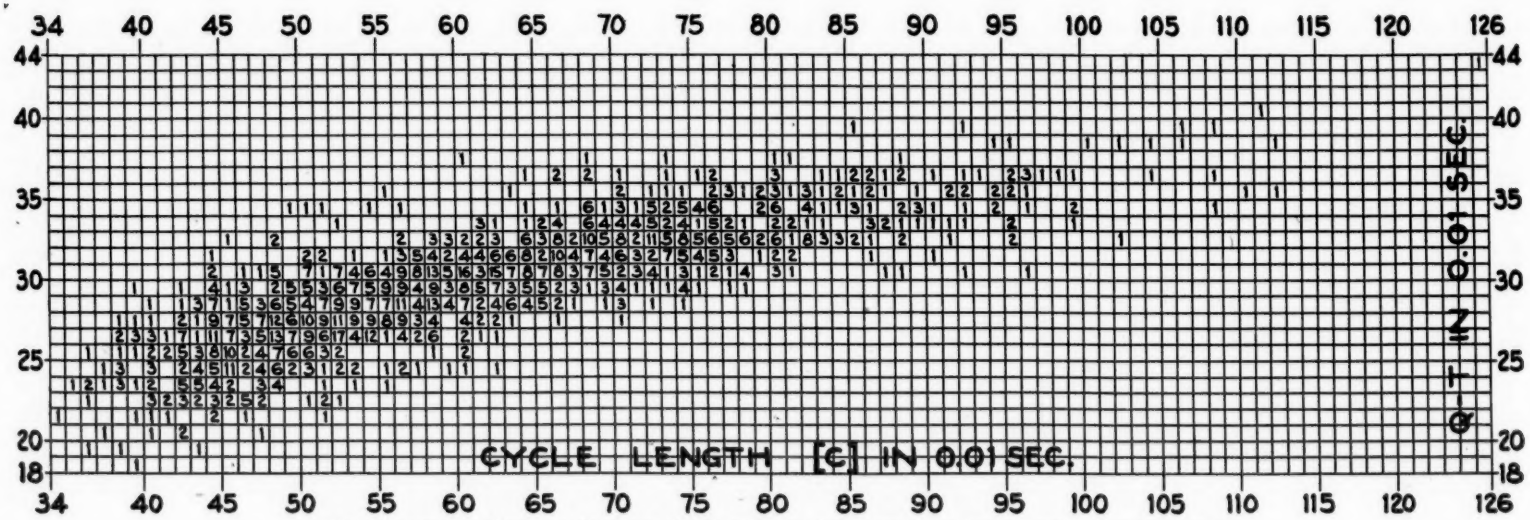


Fig. 1.—Scatter diagram showing distribution of total readings before and after exercise.

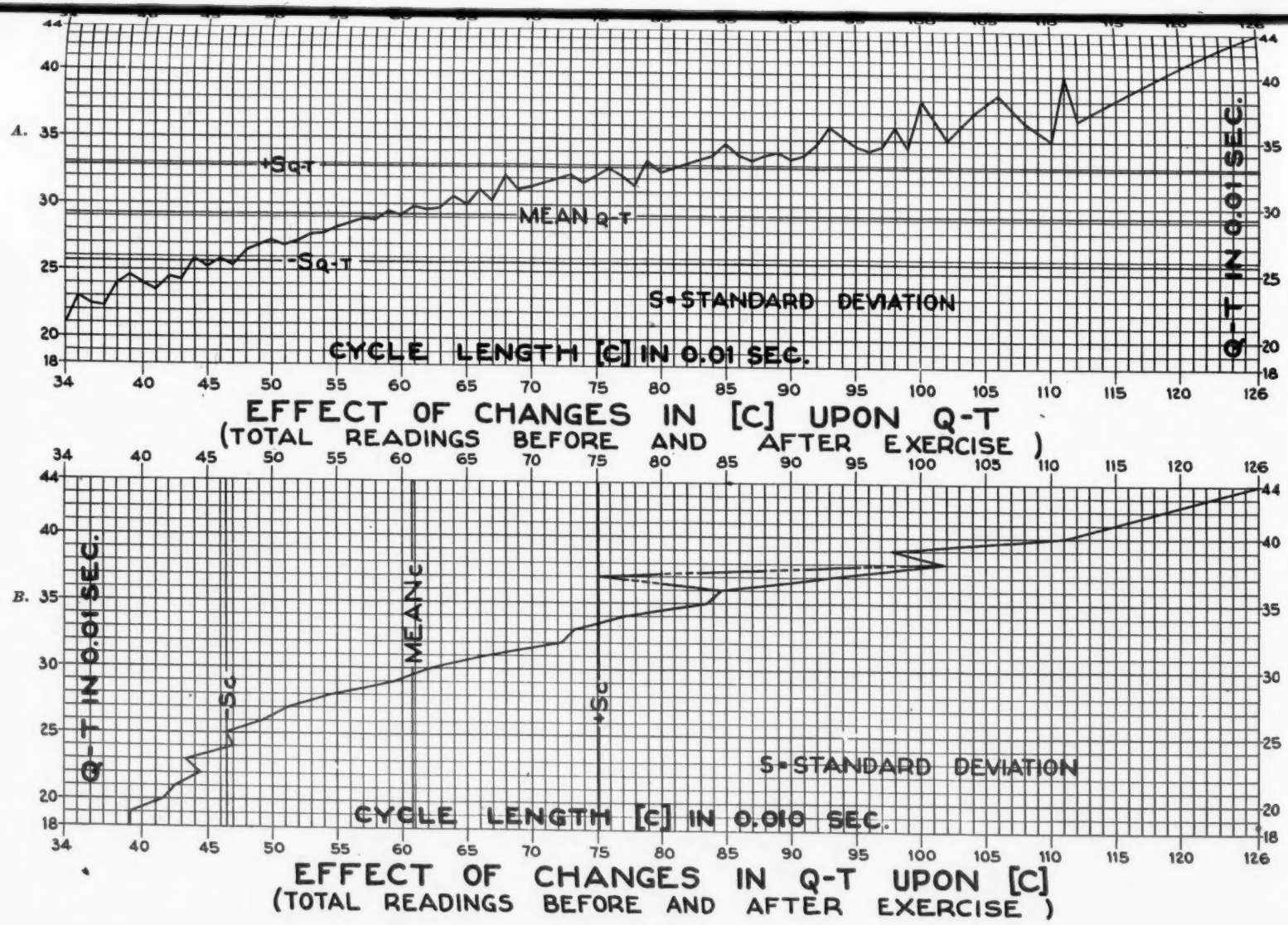

A.
+SQ-T
MEAN Q-T
-SQ-T
S=STANDARD DEVIATION
CYCLE LENGTH [C] IN 0.01 SEC.
Q-T IN 0.01 SEC.
EFFECT OF CHANGES IN [C] UPON Q-T
(TOTAL READINGS BEFORE AND AFTER EXERCISE)
B.
Q-T IN 0.01 SEC.
-Sc
MEANc
+Sc
S=STANDARD DEVIATION
CYCLE LENGTH [C] IN 0.010 SEC.
EFFECT OF CHANGES IN Q-T UPON [C]
(TOTAL READINGS BEFORE AND AFTER EXERCISE)

Fig. 2.

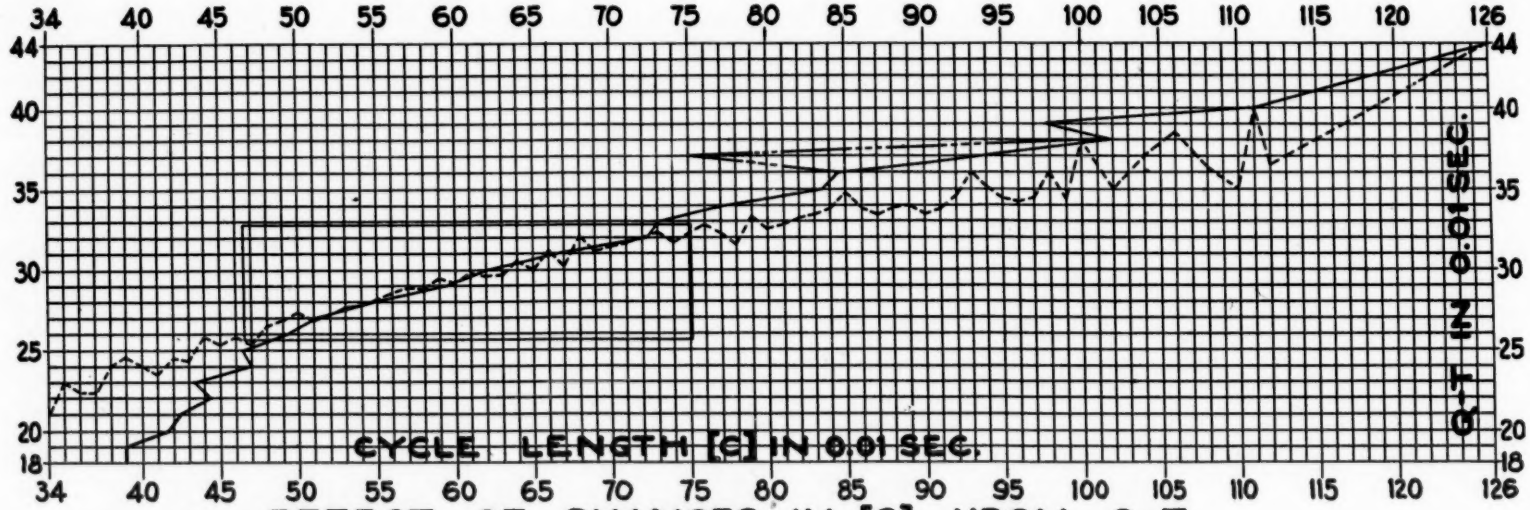

34 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 126
44 40 35 30 25 20 18
CYCLE LENGTH [C] IN 0.01 SEC.
Q-T IN 0.01 SEC.
-------- EFFECT OF CHANGES IN [C] UPON Q-T
——— EFFECT OF CHANGES IN Q-T UPON [C]
COMPOSITE CURVE FOR TOTAL READINGS BEFORE & AFTER EXERCISE

Fig. 3.

by inspection alone. Two curves were constructed: one shows the average Q-T readings for each C value (Fig. 2, *A*), thus making C the independent variable; the other (Fig. 2, *B*) shows the average C readings for each Q-T value, making Q-T the independent variable. By superimposing the two curves (Fig. 3), we see how closely the two variables depend on each other. This correlation appears to be greatest for C values from 0.465 second to 0.751 second (heart rates about 130-80 per minute), where 70.3 per cent of the readings fall; and for Q-T values from 0.256 second to 0.329 second, where 78.5 per cent of the readings fall. The Limits, which correspond to the intersection of the means plus and minus the standard deviation of C and Q-T, respectively, are shown by the box drawn in Fig. 3. This area includes 55.3 per cent of all the measurements. The degree of correlation as expressed by the coefficient of correlation[30-32] was calculated (Fig. 4) and found to be plus 0.779; a value of plus 1.000 representing perfect correlation, and a value of 0.000 representing no correlation. Therefore, this can be considered indicative of a high positive correlation.

1. Total Readings - Before & After Exercise

$$r = \frac{\Sigma XY - \frac{(\Sigma X)(\Sigma Y)}{N}}{\sqrt{\Sigma X^2 - \frac{(\Sigma X)^2}{N}}\sqrt{\Sigma Y^2 - \frac{(\Sigma Y)^2}{N}}} = \frac{257.526 - \frac{(862.490)(413.840)}{1419}}{\sqrt{553.159 - \frac{(862.490)^2}{1419}}\sqrt{112.715 - \frac{(413.840)^2}{1419}}}$$

$$r = \frac{5.988}{7.687} = +0.779$$

r = Coefficient
X = C in 0.01 Sec.
Y = Q-T in 0.01 Sec.
N = # Readings
Σ = Sum of

Fig. 4.—Determination of coefficients of correlation for variables Q-T and C.

$$K_1 = \frac{\Sigma XY - \frac{(\Sigma X)(\Sigma Y)}{N}}{\Sigma X^2 - \frac{(\Sigma X)^2}{N}}$$

K_1 = Slope
X = C in 0.01 sec.
Y = QT in 0.01 sec.
N = # Readings
Σ = Sum of

1. Total Readings Before & After Exercise

$$K_1 = \frac{5.998}{29.229} = +0.205$$

Fig. 5.—Determination of slopes of curves for Q-T and C relationship.

In Figs. 1 and 2, *A*, the relationship appears to be linear. However, there is some evidence of slight curvilinearity at each of the extremes of the curves. Since only about 10 per cent of the readings are represented by these portions of the curve, the question arose as to whether there is a significant deviation from linearity. To test for this, Fisher's method of analysis of variance[32] was used. The following fraction was arrived at:

$$F = \frac{0.0005761 \text{ Mean Square Deviation from Linear Regression}}{0.0005610 \text{ Mean Square Error within Group Means}} = 1.03,$$

with 1,344 degrees of freedom for the greater mean square, and 73 degrees of freedom for the lesser mean square. Comparison of F with the values found in Fisher's tables shows that the deviation from linear regression is not sig-

nificant, but is probably due to random sampling and to the small number of readings found at each of the extremes of the cycle range.

Since the Q-T to C relationship is linear, the equation for the straight line curve was calculated. Fig. 5 shows the determination of the slope,[30-32] and Fig. 6, *A*, shows the relationship of the curve of the actual data to the straight line curve which was derived. This calculated curve fits the data very closely. Thus the relationship of Q-T to C can be expressed:

$$Q\text{-}T = 0.205\ C + 0.167.$$

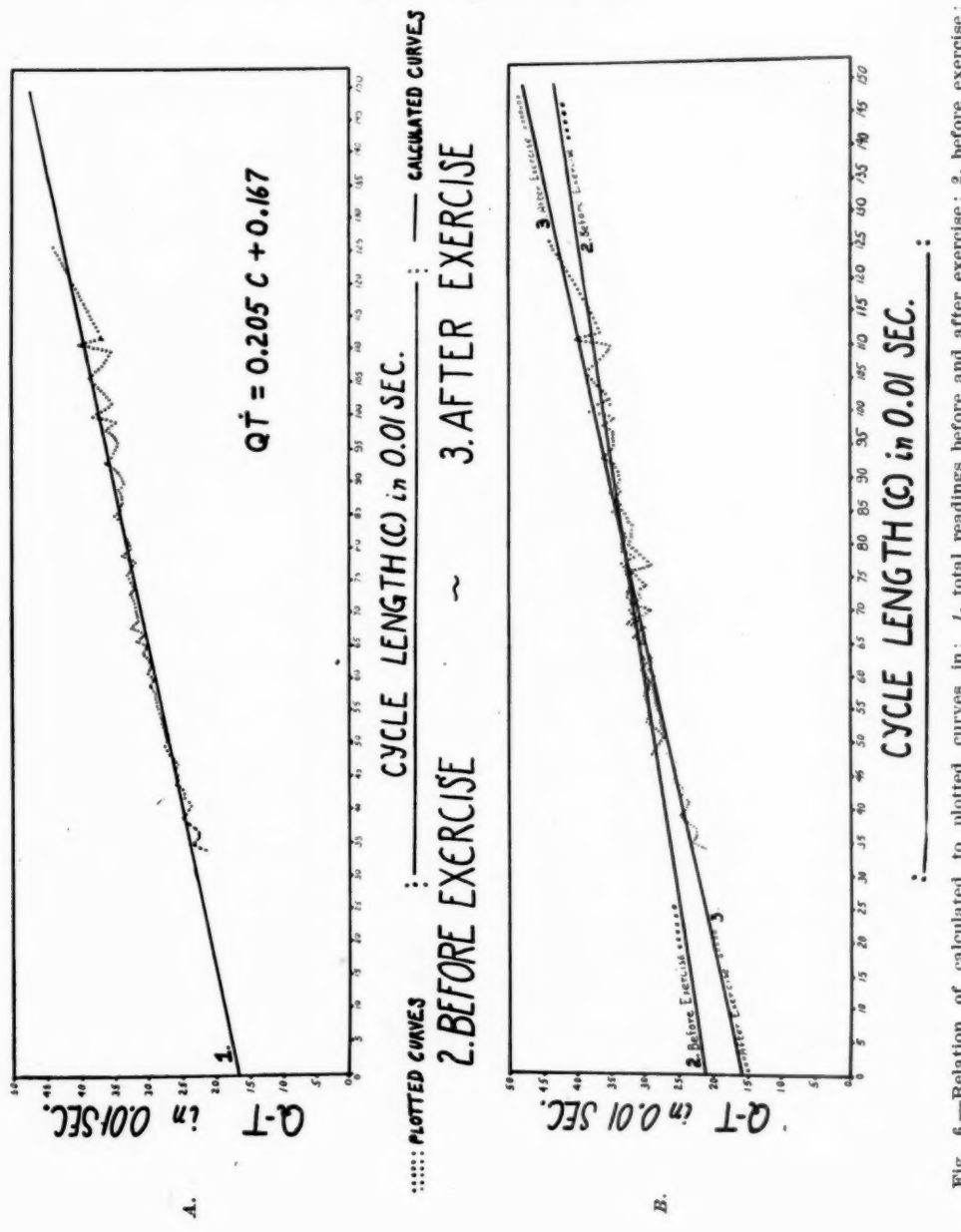


Fig. 6.—Relation of calculated to plotted curves in; *1*, total readings before and after exercise; *2*, before exercise; and *3*, after exercise.

The standard error of estimate for prediction of Q-T in this equation was found to be 0.022. The above equation can also be expressed:

$$K = \frac{Q\text{-}T - 0.167}{C}$$

where K is a constant whose value is 0.205 with a standard deviation of 0.041. Table II shows the range and distribution of K values found in all 1,419 readings. It also shows that the scatter is not very great, for K plus and minus twice the standard deviation includes 95.5 per cent of all cases. The percentage of readings that fall outside the limits set by K plus and minus three times the standard deviation, beyond which the deviation is considered significant, is small enough (1.41 per cent, 20 readings) to be considered as due to the error inherent in this study.

The data collected before and after exercise were treated in the same way as the total figures. It was found that exercise did not cause any significant

TABLE II. DISTRIBUTION OF K VALUES IN 1,419 MEASUREMENTS

K	NO.	K	NO.	K	NO.	K	NO.	K	NO.
0.034	1	0.146	3	0.185	21	0.221	8	0.261	3
0.054	1	0.147	7	0.186	23	0.222	29	0.262	1
0.061	1	0.149	2	0.187	10	0.223	23	0.263	5
0.064	1	0.150	7	0.188	17	0.224	6	0.264	5
0.071	1	0.151	1	0.189	18	0.225	17	0.266	7
0.072	1	0.152	8	0.190	17	0.226	10	0.267	10
0.078	2	0.153	1	0.191	10	0.227	16	0.269	1
0.085	1	0.155	2	0.192	12	0.228	7	0.270	2
0.090	1	0.156	6	0.193	16	0.229	22	0.272	2
0.094	1	0.157	3	0.194	29	0.230	13	0.273	1
0.097	2	0.158	2	0.195	24	0.231	8	0.275	1
0.102	1	0.159	2	0.196	15	0.232	22	0.277	5
0.104	2	0.160	12	0.197	7	0.233	17	0.278	1
0.105	1	0.161	6	0.198	26	0.234	13	0.279	4
0.106	1	0.162	12	0.199	18	0.235	10	0.281	2
0.107	1	0.163	5	0.200	1	0.236	4	0.283	3
0.110	1	0.164	8	0.201	17	0.237	8	0.286	2
0.113	2	0.165	5	0.202	36	0.238	12	0.289	1
0.114	1	0.166	23	0.203	4	0.239	22	0.291	1
0.115	5	0.168	2	0.204	10	0.240	6	0.292	3
0.118	3	0.169	10	0.205	23	0.241	15	0.294	1
0.119	1	0.170	4	0.206	17	0.242	3	0.298	1
0.120	3	0.171	10	0.207	14	0.245	4	0.302	3
0.122	1	0.172	6	0.208	8	0.246	16	0.314	1
0.124	4	0.173	13	0.209	12	0.247	15	0.316	1
0.126	3	0.174	22	0.210	23	0.248	1	0.319	2
0.128	1	0.175	8	0.211	22	0.250	1	0.321	1
0.131	6	0.176	4	0.212	22	0.251	20	0.325	1
0.132	4	0.177	12	0.213	13	0.252	1	0.332	1
0.134	3	0.178	9	0.214	16	0.254	10	0.339	1
0.138	2	0.179	27	0.215	27	0.255	3	0.340	2
0.139	3	0.180	7	0.216	8	0.256	17	0.346	1
0.140	2	0.181	5	0.217	20	0.257	1	0.353	1
0.141	2	0.182	4	0.218	12	0.258	1	0.416	3
0.143	5	0.183	11	0.219	12	0.259	3	0.434	2
0.144	2	0.184	14	0.220	15	0.260	1	0.470	1

$K = \frac{QT - 0.167}{C}$; S.D. = Standard deviation = 0.041.
K = 0.205.
0.205± S.D. include 77.7 per cent of all measurements.
0.205± 2 S.D. include 95.5 per cent of all measurements.
0.205± 3 S.D. include 98.6 per cent of all measurements.

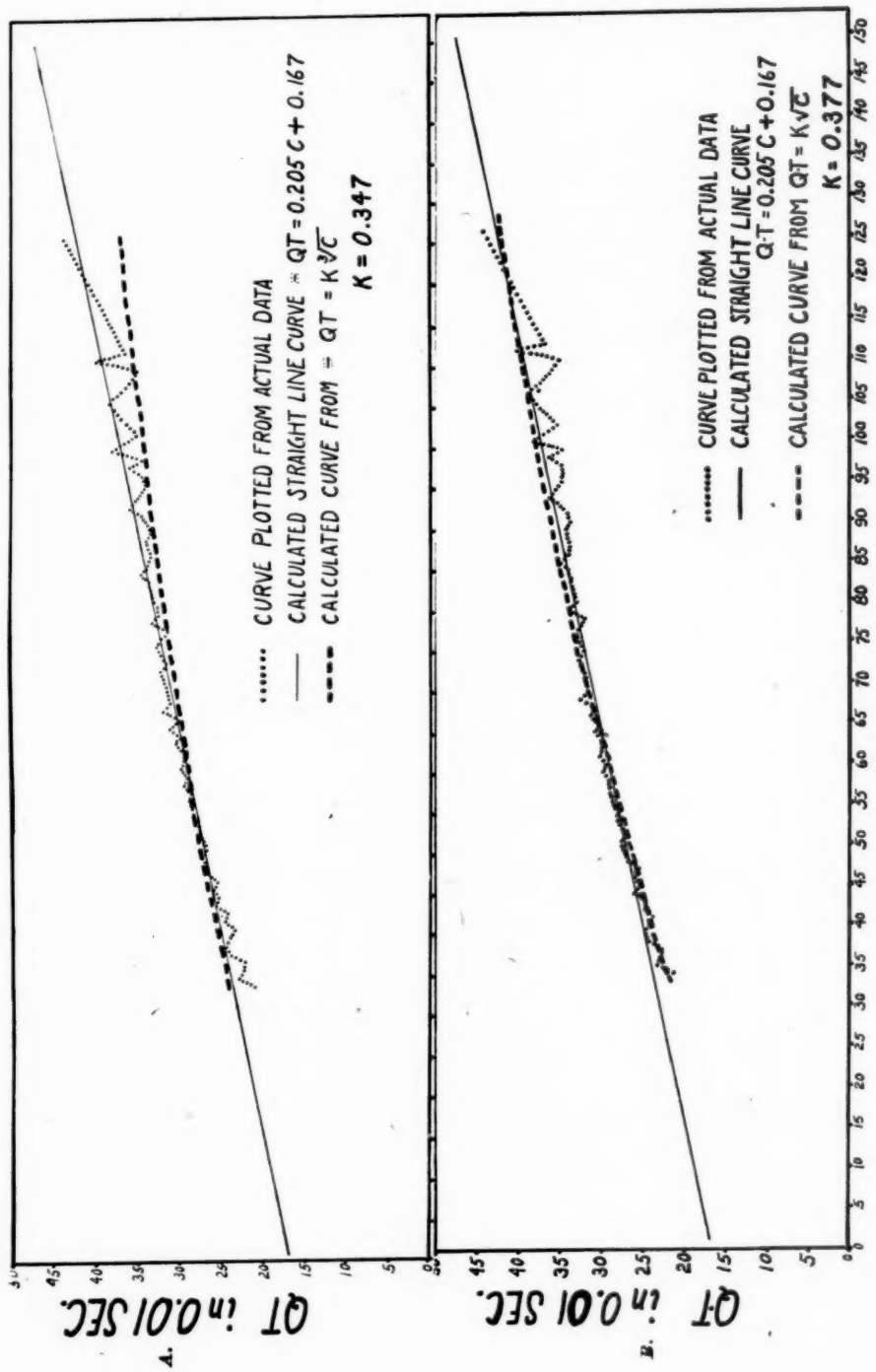

A.
QT in 0.01 SEC.
CURVE PLOTTED FROM ACTUAL DATA
CALCULATED STRAIGHT LINE CURVE = QT = 0.205 C + 0.167
CALCULATED CURVE FROM = QT = K ∛C
K = 0.347
B.
QT in 0.01 SEC.
CURVE PLOTTED FROM ACTUAL DATA
CALCULATED STRAIGHT LINE CURVE
Q-T = 0.205 C + 0.167
CALCULATED CURVE FROM QT = K√C
K = 0.377
CYCLE LENGTH (C) in 0.01 SEC.

Fig. 7.—Comparison of calculated curves of Q-T and C length relationship to each other and to the plotted curve.

change in the relationship of Q-T to C. Fig. 6, *B*, shows the actual data and the calculated curves, both before and after exercise.

A comparison was made of our data and equation with the formulas proposed by previous workers. Fig. 7, *A*, shows the curve derived from the equation, $Q\text{-}T = K\sqrt[3]{C}$, which was proposed by Fridericia. Fridericia used the value 8.22 for K, which he obtained by multiplying the Q-T and C values by 100 before using them in his equation. This value of 8.22 is equivalent to 0.381 when the readings are not multiplied by 100. It was found that the curve did not approximate the data until a new value for K was calculated. This was found to be 0.347. Despite this new value for K, the curve does not fit the data so well as do the curves proposed by other workers. Fig. 7, B, shows the curve derived from Bazett's equation, $Q\text{-}T = K\sqrt{C}$, superimposed on the actual data and the straight line curve. The value of K had to be adjusted from 0.37 to 0.377 to give us this fit. Apparently this formula fits the data best at the more rapid heart rates.

Fig. 8, *A*, shows the curve derived from Ashman's equation, $Q\text{-}T = K \log [10(C + k)]$, where K is 0.375, and k is 0.07, as proposed by the author. This curve deviates from both the data and the straight line curve, primarily because Ashman's Q-T measurements are slightly longer than those recorded herein. However, by recalculating the value of K in all 1,419 readings, it was found that with the use of 0.354 as the value of K, the relationship shown in Fig. 8, *B*, is obtained. This curve appears to fit the data much better than the straight line curve. It was therefore decided to test this to determine if there actually was a significant deviation from the linear curve. This was done by testing for significance of the deviation of the curvilinear regression from the linear regression, with the former represented by Ashman's equation. Fisher's method of analysis of variance[32] was used and the following fraction was obtained:

$$F = \frac{0.0021 \text{ Mean Square of Curvilinearity of Regression}}{0.000456 \text{ Mean Square of Deviation from Curvilinear Regression}} = 4.61,$$

with 1 degree of freedom for the greater mean square, and 72 degrees of freedom for the lesser mean square. Comparison of F with the values found in Fisher's tables shows that the deviation from linear regression is not significant. Therefore, this curvilinear regression is not a better fit, statistically, than the linear regression. This test of the significance of departure from linearity, as well as the one previously outlined (i.e., a test of deviation of the original data from linearity) indicates that the Q-T to C relationship is linear, and that curving both extremes of the curve to fit the small number of readings represented there is not warranted.

Although Adams' formula is a straight line one, his slopes and constants are at marked variance with those found in this study. This variance might be explained by the fact that in his study he used only 50 men and 54 women, instead of a larger sample of the population.

The curve arrived at herein, as well as all those previously proposed, are really the composites of the curves derived from the measurements of the electro-

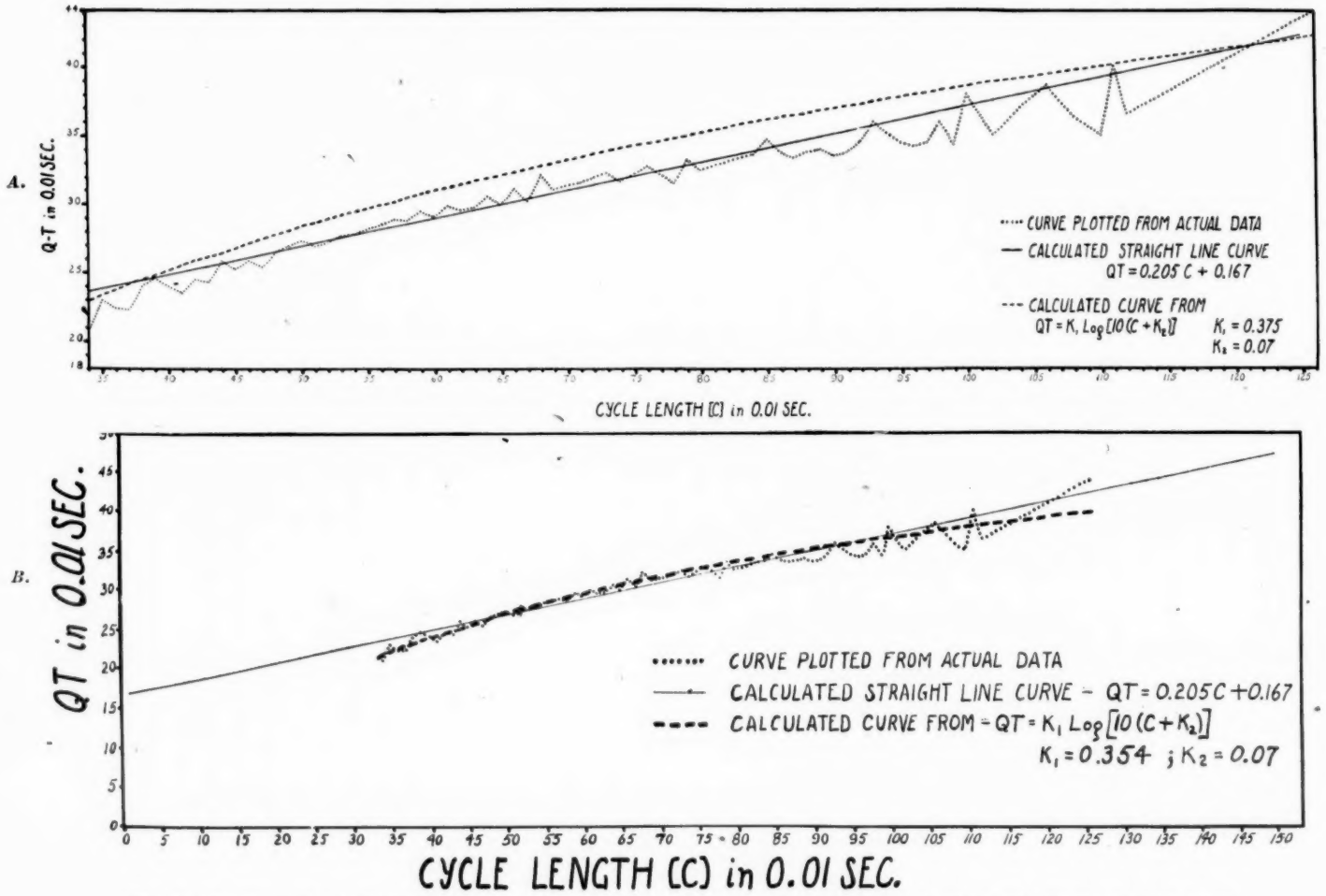

A.
Q-T in 0.01 SEC.
CURVE PLOTTED FROM ACTUAL DATA
CALCULATED STRAIGHT LINE CURVE
QT = 0.205 C + 0.167
CALCULATED CURVE FROM
QT = K, Log [10 (C + K2)]
K, = 0.375
K2 = 0.07
CYCLE LENGTH (C) in 0.01 SEC.
B.
QT in 0.01 SEC.
CURVE PLOTTED FROM ACTUAL DATA
CALCULATED STRAIGHT LINE CURVE - QT = 0.205C + 0.167
CALCULATED CURVE FROM - QT = K1 Log [10 (C + K2)]
K1 = 0.354 ; K2 = 0.07
CYCLE LENGTH (C) in 0.01 SEC.

Fig. 8.—Comparison of calculated curves of Q-T and C length relationship to each other and to the plotted curve.

cardiograms of many individuals. Therefore, it is expected that variations from the mean value will occur when the formulas are applied to the individual case. These variations remain within the limits of values comprising the normal scatter. Measurements in the individual case made at various cycle lengths, and plotted on a curve, also approximate the composite curve in type, and the deviation remains within the normal limits.

The effects of various factors, for example, carditis, cardiac hypertrophy, change of position and drugs, were not included in this study. It is therefore not yet possible to predict the value of the application of this curve and this constant for detecting physiologic or organic disturbances of the heart.

It is noteworthy that the length of the measurements varies with different workers. Shipley and Hallaran's[15] and Ashman's[22] measurements are longer than those included in this study, whereas White and Mudd's[9] measurements are in close agreement with those reported herein. This may account for the differences in the values proposed by the different authors for the constant (K).

Statistical methods were applied in the study of the data, not for the purpose of proving anything, but to test and analyze the data objectively. It was believed that the large number of readings warranted the use of these methods.

CONCLUSIONS

1. In normal young men, there is a constant relationship, with a significant positive correlation, between the Q-T interval and the cycle length.

2. This relationship is linear and can be expressed by the equation:

$$Q\text{-}T = 0.205\ C + 0.167$$

or

$$K = \frac{Q\text{-}T - 0.167}{C}$$

where K is 0.205, with a standard deviation of 0.041.

3. Tachycardia produced by exercise in normal young men does not change this relationship.

The author wishes to express his appreciation to Dr. Guy Stevenson, Head of the Department of Mathematics and Acting Director of the Graduate School, University of Louisville, Louisville, Ky., for his helpful criticisms and for suggestions on the statistical analyses used in the preparation of this paper.

REFERENCES

1. Lombard, W. P., and Cope, O. M.: Effect of the Pulse Rate on the Length of the Systoles and Diastoles of the Normal Human Heart in the Standing Position, Am. J. Physiol. **49**: 139, 1919.
2. Lombard, W. P., and Cope, O. M.: Effect of Posture on the Length of the Systole of the Human Heart, Am. J. Physiol. **49**: 140, 1919.
3. Bazett, H. C.: An Analysis of the Time Relations of Electrocardiograms, Heart **7**: 353, 1920.
4. a. Fridericia, L. C.: Die Systolendauer Im Elektrokardiogramm bei normalen Menschen und bei Herzkranken, I and II, Acta med. Scandinav. **53**: 469, 1920.
   b. Ibid. **54**: 17, 1920-1921.
5. Katz, Louis N.: Factors Modifying the Duration of Ventricular Systole, J. Lab. & Clin. Med. **6**: 291, 1921.
6. Fenn, G. K.: Studies in the Variation of the Length of the Q-R-S-T Interval, Arch. Int. Med. **29**: 441, 1922.

7. Miki, Y.: Experimentelle und Klinische Untersuchunger über die Dauer des Kammer-Elektrokardiogramms, Ztschr. f. d. ges. exper. Med. **27**: 323, 1922.
8. Bazett, H. C., and Sands, J.: The Significance of Measurements of the Duration of Systole, Ann. Clin. Med. **5**: 190, 1926.
9. White, P. D., and Mudd, S. G.: Observations on the Effect of Various Factors on the Duration of the Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram, J. Clin. Investigation **7**: 387, 1929.
10. Cheer, S. M., and Li, R. C.: Studies on the Electrical Systole (Q-T Interval) of the Heart. I. Duration of Electrical Systole in Normal Chinese, Chinese J. Physiol. **4**: 191, 1930.
11. Cheer, S. M., and Dieuaide, F. R.: Studies on the Electrical Systole (Q-T Interval) of the Heart. II. Its Duration in Cardiac Failure, J. Clin. Investigation **10**: 889, 1931.
12. Berliner, Kurt: Observations on the Duration of the Electrical Systole of the Heart, With Special Reference to the Effect of Digitalis, AM. HEART J. **7**: 189, 1931.
13. Cheer, S. M., and Dieuaide, F. R.: Studies on the Electrical Systole (Q-T Interval) of the Heart, J. Clin. Investigation **11**: 1241, 1932.
14. Adams, Wright: The Normal Duration of the Electrocardiographic Ventricular Complex, J. Clin. Investigation **15**: 335, 1936.
15. Shipley, R. A., and Hallaran, W. R.: The Four Lead Electrocardiogram in 200 Normal Men and Women, AM. HEART J. **11**: 324, 1936.
16. Hafkesbring, E. M., Drawe, C. E., and Ashman, R.: Children's Electrocardiograms. I. Measurements for One Hundred Normal Children, Am. J. Dis. Child. **53**: 1457, 1937.
17. Drawe, C. E., Hafkesbring, E. M., and Ashman, R.: Children's Electrocardiograms. II. The Changes in Children's Electrocardiograms Produced by Rheumatic and Congenital Heart Disease, Am. J. Dis. Child. **53**: 1470, 1937.
18. Barker, P. S., Johnston, F. D., and Wilson, F. N.: Duration of Systole in Hypocalcemia, AM. HEART J. **14**: 82, 1937.
19. Ashman, Richard: Normal Duration of the Q-T Interval, Proc. Soc. Exper. Biol. & Med. **40**: 150, 1939.
20. Blair, H. A., Wedd, A. M., and Young, A. C.: The Relation of the Q-T Interval to the Refractory Period, the Diastolic Interval, the Duration of Contraction and the Rate of Beating in Heart Muscle, Am. J. Physiol. **132**: 157, 1941.
21. Ashman, R., and Hull, E.: Essentials of Electrocardiography, ed. 2, New York, 1941, The Macmillan Co.
22. Ashman, Richard: The Normal Duration of the Q-T Interval, AM. HEART J. **23**: 522, 1942.
23. White, M. S., Kossmann, C. E., and Ershler, I. The Effect of High Altitude and Rebreathing on the Duration of Electrical Systole in Man, AM. HEART J. **24**: 230, 1942.
24. Phang, S. H., and White, P. D.: The Duration of Ventricular Systole as Measured by the Q-T Interval of the Electrocardiogram, With Especial Reference to Cardiac Enlargement With and Without Congestive Failure, AM. HEART J. **26**: 108, 1943.
25. Viscidi, P. C., and Geiger, A. J.: Electrocardiographic Observations on 500 Unselected Young Adults at Work, AM. HEART J. **26**: 763, 1943.
26. Stewart, C. B., and Manning, G. W.: A Detailed Analysis of the Electrocardiograms of 500 R. C. A. F. Aircrew, AM. HEART J. **27**: 502, 1944.
27. Graybiel, A., McFarland, R. A., Gates, D. C., and Webster, E. A.: Analysis of the Electrocardiograms Obtained From 1000 Young Healthy Aviators, AM. HEART J. **27**: 524, 1944.
28. Albers, D.: Zur Analyse der QRS Gruppe im menschlichen Elektrokardiogramm, Ztschr. f. Kreislaufforsch. **32**: 265, 1940.
29. Ohr, A., and Porscha, W.: Beitrag zur QT und PQ Dauer im Ekg des Kindersalters, Ztschr. f. Kreislaufforsch. **32**: 809, 1940.
30. Granville, W. A., Smith, P. F., and Longley, W. R.: Elements of the Differential and Integral Calculus, revised edition, New York, 1941, Ginn and Company.
31. Walker, H. M.: Elementary Statistical Methods, New York, 1943, Henry Holt and Company.
32. Snedecor, G. W.: Statistical Methods, ed. 3, Ames, 1940, The Iowa State College Press.

THE PERIPHERAL BLOOD FLOW UNDER BASAL CONDITIONS IN OLDER MALE SUBJECTS WITH NORMAL AND ELEVATED BLOOD PRESSURES

HAROLD J. STEWART, M.D., WILLIS F. EVANS, M.D., AND HELEN S. HASKELL, M.D.
NEW YORK, N. Y.

IN RECENT years, the peripheral circulation has been the subject of new interest because of the added attention which has been given to inflammatory, occlusive, and vasospastic states of the peripheral vessels. We have been interested in that part of the volume output of blood from the heart which is allotted to the peripheral circulation. In studies of normal male subjects in the earlier decades we found that 73 c.c. per square meter of body surface per minute was the average amount of blood allotted to the peripheral circulation in a room at 27° C. with a humidity of 50 per cent.[1] However, this was reduced to 52 c.c. per square meter of body surface per minute when the room temperature was 25° C. The differences which are encountered in the peripheral blood flow of subjects in the later decades who had clear-cut evidences of vascular disease form the basis of this report. The clinical diagnoses shown in Table I indicate that these patients exhibited a wide range of generalized vascular disease, such as arteriosclerotic heart disease, hypertension, coronary artery disease, angina pectoris, coronary thrombosis, and generalized arteriosclerosis.

The peripheral blood flow has been measured on 27 occasions in 25 male subjects from 38 to 77 years of age. The blood pressure was in the normal range in 12 subjects and was elevated in 13 subjects; these groups are designated as the "normal blood pressure group" and the "hypertensive group," respectively.

METHODS

Measurements of peripheral blood flow were made by modifying the method of Hardy and Soderstrom[2] in such a way that the use of a calorimeter was not necessary. This modification has been described previously.[3-5] The following data are required: skin temperatures at eleven points on the anterior surface of the body, as shown in Fig. 1[3]; rectal temperature; oxygen consumption; height; and body weight. In this method is measured the amount of blood allotted to the periphery of the whole body to a depth of 1 cm. below the surface. Blood pressure and pulse rate are recorded.

The skin temperatures were measured with the Hardy-Soderstrom radiometer[6]; the rectal temperature was measured with a single-junction, copper-constantan thermocouple[6]; and the oxygen consumption was measured with a

From the Department of Medicine of the New York Hospital and the Cornell University Medical College, New York, New York. Supported by a grant from the John and Mary R. Markle Foundation.

TABLE I. DATA RELATING TO TWENTY-FIVE MALE PATIENTS FROM 38 TO 77 YEARS OF AGE, EXHIBITING VASCULAR DISEASE, AT ROOM TEMPERATURE OF 27° C.

CASE AGE (YRS.) HISTORY NO.	PERIPHERAL BLOOD FLOW (C.C./M.²/MIN.)	AVERAGE RECTAL TEMPERATURE °C.	AVERAGE WEIGHTED SKIN TEMPERATURE °C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRESSURE MM. HG	PULSE RATE PER MIN.	BASAL METABOLIC RATE PER CENT	DIAGNOSIS
				1 °C.	2 °C.	3 °C.	4 °C.	5 °C.	6 °C.	7 °C.	8 °C.	9 °C.	10 °C.	11 °C.				
Normal Blood Pressure Group																		
N. H. 53 275880	53	37.58	34.16	35.3	34.9	34.4	34.2	34.4	34.7	35.2	33.8	32.9	33.3	33.6	107/65	75	- 8	Arteriosclerotic heart disease. Angina pectoris. Anemia
D. G. 63 83994	81	36.89	34.19	35.1	34.7	34.3	34.6	33.9	33.7	34.4	34.3	33.2	33.7	34.3	115/75	65	- 9	Arteriosclerotic heart disease. Coronary thrombosis
J. S. 52 158786	39	36.91	34.12	35.0	34.7	34.3	34.7	34.4	34.7	35.0	33.7	33.6	32.7	33.5	149/75	55	- 1	Arteriosclerotic heart disease. Enlarged heart
M. K. 67 352240	114	36.94	33.44	34.7	34.7	33.7	33.8	33.8	33.8	33.8	33.3	32.4	32.1	32.0	120/79	63	+30	Arteriosclerotic heart disease. Coronary artery disease. Enlarged heart
N. M. 38 357527	166	37.18	34.45	35.7	35.3	35.1	35.4	34.5	34.6	35.3	34.3	33.8	32.7	32.4	108/68	70	+37	History of fluctuation in blood pressure and of being high in last two years
F. S. 54 342341	56	37.32	34.54	35.5	35.5	35.3	35.2	34.9	34.3	34.9	34.5	32.4	33.6	34.0	148/90	72	- 5	Hypertensive heart disease. Angina pectoris. Auricular fibrillation
H. S. 70 61672	84	36.40	33.48	34.6	34.0	33.4	33.4	33.2	32.9	34.5	32.4	33.3	32.9	33.8	107/64	62	-0.4	Arteriosclerotic heart disease. Coronary artery disease. Angina pectoris. Enlarged heart
A. K. 81 230574	62	36.70	33.79	34.4	34.3	33.9	34.2	33.4	33.3	34.8	34.0	32.8	32.9	33.8	127/61	56	+ 4	Arteriosclerotic heart disease. Coronary thrombosis. Generalized arteriosclerosis
C. T. 52 355770	47	37.20	34.60	35.2	35.0	34.8	35.2	34.7	34.0	34.7	34.6	34.5	33.8	33.9	115/64	60	- 4	Arteriosclerotic heart disease. Enlarged heart. Auricular fibrillation. Pulmonary fibrosis
L. M. 65 255998	46	37.13	33.60	34.7	34.8	33.4	34.9	35.6	33.2	35.0	32.4	34.1	31.6	32.1	132/70	71	+36	Arteriosclerotic gangrene of the right foot. Observation 41 days after amputation

V. B. 54 364494	49	36.89	33.43	33.8	34.3	34.1	33.6	34.4	33.5	34.4	32.6	32.8	31.3	33.1	108/68	53	- 7	Arteriosclerotic heart disease. Coronary thrombosis
F. C. 54 106423	79	36.78	34.10	34.4	34.7	34.3	34.0	34.2	33.7	34.8	33.7	33.9	33.1	35.1	152/98	73	+10	Hypertensive heart disease. Enlarged heart. Cerebral thrombosis. Arteriosclerosis
Average	73	36.95	33.99	34.9	34.7	34.3	34.4	34.1	33.9	34.7	33.6	33.3	32.8	33.4	124/73	65	+ 7	
Standard deviations about the means	35	0.30	0.41	0.5	0.4	0.6	0.6	0.5	0.6	0.4	0.8	0.7	0.8	0.9	17/11	7	14	
								Hypertension Group									
W. M. 69 212967	57	36.82	33.83	35.2	33.3	34.5	34.2	33.8	33.6	34.1	33.5	33.5	33.0	32.0	186/100	70	+15	Hypertensive and arteriosclerotic heart disease. Enlarged heart. Coronary artery disease
J. O'K.	77	37.68	34.28	35.5	35.2	35.4	35.3	34.7	34.4	35.1	34.3	33.1	32.4	32.0	181/126	88	+19	Hypertensive cardiovascular heart disease
40 231295	23	37.44	34.36	35.5	35.2	35.5	35.4	34.7	34.6	35.4	34.3	33.1	32.0	32.3	181/117	75	-12	
C. W. 48 331023	80	37.24	33.55	34.3	34.8	34.1	34.8	34.6	34.0	31.2	38.3	32.5	31.8	30.0	188/116	85	+ 3	Hypertensive cardiovascular heart disease
H. V. 40 281681	49	37.59	33.96	34.9	34.6	35.1	34.9	34.4	33.9	34.2	34.7	32.8	32.8	30.8	173/136	82	+22	Arteriosclerosis. Hypertensive cardiovascular heart disease. Coronary artery disease
G. W. 48 386933	28	37.67	33.06	34.7	34.4	34.0	33.8	33.8	33.6	33.9	32.4	30.9	31.1	31.6	251/162	98	+34	Arteriolarnephrosclerosis. Hypertensive cardiovascular disease. Enlarged heart. Aortic insufficiency. Myocardial infarction
C. C. 40 386438	48	37.06	33.90	35.2	34.9	34.2	33.7	34.2	34.4	35.0	32.8	32.9	32.6	34.4	218/139	39	+ 5	Essential hypertension. Renal arteriosclerosis
R. R. 47 388459	35	37.73	33.94	35.7	35.5	34.9	34.5	34.6	34.1	35.3	32.8	32.7	32.2	31.3	217/131	80	+13	Hypertensive cardiovascular heart disease

TABLE I.—CONT'D

CASE AGE (YRS.) HISTORY NO.	PERIPHERAL BLOOD FLOW (C.C./M.²/MIN.)	AVERAGE RECTAL TEMPERATURE °C.	AVERAGE WEIGHTED SKIN TEMPERATURE °C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRESSURE MM. HG	PULSE RATE PER MIN.	BASAL METABOLIC RATE PER CENT	DIAGNOSIS
				1 °C.	2 °C.	3 °C.	4 °C.	5 °C.	6 °C.	7 °C.	8 °C.	9 °C.	10 °C.	11 °C.				
Hypertension Group—Cont'd																		
S. McD. 48 95209	25	37.11	33.52	34.9	34.5	33.7	33.5	33.9	33.6	34.2	33.1	32.2	33.0	32.5	177/133	68	-11	Hypertensive cardiovascular heart disease
W. C. 48 375325	62	37.27	34.30	35.3	35.1	34.5	34.7	34.4	34.2	35.0	33.7	33.5	33.2	34.4	198/113	66	- 1	Hypertensive cardiovascular heart disease. Myocardial infarction. Arteriosclerosis. Coronary thrombosis
	70	37.10	33.97	35.0	34.8	34.3	34.3	33.8	34.2	34.8	32.9	33.2	32.9	34.5	193/112	66	0	
J. S. 44 353263	21	37.46	33.86	35.0	34.4	34.2	34.4	34.0	33.9	34.8	33.5	32.6	32.6	33.4	211/126	62	+ 4	Hypertensive heart disease. Coronary thrombosis
P. L. 53 384879	79	37.40	33.71	34.0	34.8	33.8	34.6	33.7	33.0	34.5	33.2	33.1	32.3	34.1	197/103	83	+20	Chronic pyelonephritis. Hypertensive heart disease. Coronary artery disease
H. S. 77 109660	87	37.30	33.80	35.1	35.4	34.8	34.9	34.3	34.4	34.2	33.1	33.0	31.8	31.4	176/87	72	+36	Hypertension. Arteriosclerotic heart disease. Auricular fibrillation
B. C. 69 377456	91	37.01	34.35	35.0	35.0	34.9	35.4	34.5	34.0	34.4	34.8	33.5	33.2	32.8	163/91	74	+23	Hypertension. Arteriosclerotic heart disease
Average	55	37.32	33.92	35.0	34.8	34.5	34.6	34.2	34.0	34.4	33.5	32.8	32.5	32.6	194/117	77	+ 9	
Standard deviations about the means	24	0.26	0.35	0.4	0.5	0.5	0.6	0.4	0.4	1.0	1.4	0.6	0.6	1.4	22/19	10	14	
Average from both groups	63	37.18	33.93	34.9	34.8	34.4	34.5	34.2	33.9	34.6	33.5	33.0	32.6	32.9	156/98	72	+ 9	
Standard deviations both groups about the means	31	0.39	0.38	0.5	0.5	0.6	0.6	0.4	0.5	0.8	1.2	0.7	0.7	1.3	41/27	11	15	
*Normal Subjects in Third Decade**																		
Average	73	36.79	33.74	34.4	34.2	34.1	34.2	33.8	33.7	34.4	33.2	33.2	33.2	32.7	105/71	61	- 5	
Standard deviations about the means	30	0.16	0.33	0.3	0.4	0.5	0.5	0.5	0.5	0.5	0.7	0.7	0.5	1.9	5/5	7	10	

*Stewart and Evans.[1]

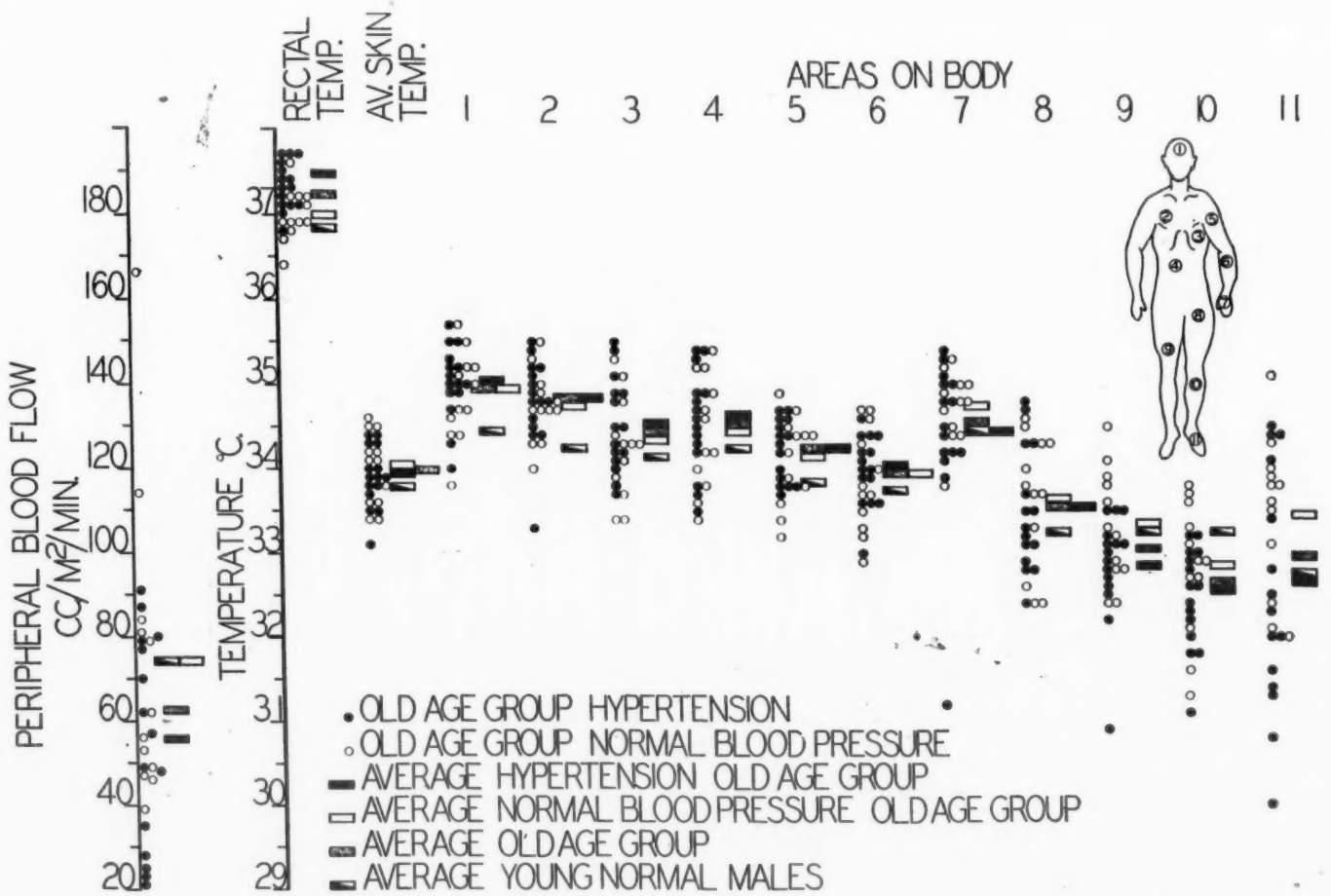


Fig. 1.—In this figure are shown the peripheral blood flow, rectal temperature, average weighted skin temperature, and temperature of 11 areas on the anterior surface of the body in 25 patients from 38 to 77 years of age. Open circles represent those with normal blood pressure, and closed circles represent those with hypertension. The averages for all patients in each category are shown by appropriate symbols. The averages for normal young male subjects[1] are shown for comparison.

Benedict-Roth metabolism apparatus.[7] The basal metabolic rate was calculated from the Mayo Foundation standards for age and sex,[8] and the surface area was calculated from the tables of DuBois and DuBois.[9]

PROCEDURE

All observations were made in the morning, when the patients were in a basal metabolic state. The rectal thermometer was inserted to a depth of 10 cm. as soon as the patient reached the constant temperature room and remained in place during the morning's observations. The subjects lay nude in bed, covered only with a sheet. The room temperature was maintained at or near 27° C., and the humidity ranged between 45 and 50 per cent. In order to become accommodated to this environment, the patients lay at rest for one hour before observations were started. Three to eight sets of observations were made, from which it was possible to make two to seven calculations of peripheral blood flow. In some instances the oxygen consumption was measured at the end as well as at the beginning of the observations. In some instances ten-minute and, in others, twenty-minute intervals were chosen for making the measurements of skin temperatures, and the formulas used in making the calculations were adjusted accordingly.[5]

OBSERVATIONS

The results of the observations are shown in Table I and Fig. 1.

Peripheral Blood Flow.—The data are recorded in Table I, and the scatter diagram of the peripheral blood flow calculations is shown in Fig. 1. On the whole, the peripheral blood flow in the group with normal blood pressure was greater than in the group with elevated blood pressure, although there was some overlapping. The average peripheral blood flow for the normal blood pressure group was 73 c.c. per square meter of body surface per minute, the same as that found in normal young individuals at this temperature.[1] In the group with hypertension, however, it was only 55 c.c. per square meter of body surface per minute, or approximately the same as that found in normal subjects at the lower room temperature of 25° C. The average for the combined groups was 63 c.c. per square meter of body surface per minute.

Rectal Temperature.—The average rectal temperature for the group with normal blood pressure was 36.95° C.; for the group with hypertension, 37.32° C.; and for the combined groups, 37.18° C. (Table I, Fig. 1). Therefore, the rectal temperature of the group with hypertension was 0.37° C. higher, on an average, than that of the group with normal blood pressure, and in both groups the rectal temperature was higher than it was in normal young men, in whom it averaged 36.79° C.

Weighted Skin Temperature.—The weighted skin temperature averaged 33.99° C. for the group with normal blood pressure and 33.92° C. for the group with hypertension; it was 33.93° C. for the groups combined, as compared with 33.40° C. for the group of normal young men (Table I, Fig. 1). In short the average skin temperature was higher in this older age group with vascular disease than in the younger normal subjects.

Temperatures of the Hands.—The average of the temperatures of the hands (Area 7) was 34.7° C. for the group of older subjects with normal blood pressure and 34.4° C. for the group with hypertension. That is to say that the average hand temperatures in the older group with normal blood pressure are slightly higher than those in the group of normal young men, whose hand temperatures averaged 34.4° C. In the group with hypertension the average hand temperature of 34.4° C. was the same as that in the normal group.

Temperatures of the Feet.—The average of the temperatures of the feet was 33.4° C. for the group of older subjects with normal blood pressure and 32.6° C. for the hypertension group (Table I, Fig. 1). The feet were therefore warmer in the group with normal blood pressure than in the group of normal young men in which the temperatures of the feet averaged 32.7° C.; in the hypertension group the temperatures of the feet were slightly below normal.

Temperatures of Other Areas of the Body.—For Areas 1 to 6, inclusive, of the body surface, that is, for the upper part of the body, the skin temperature was higher in the hypertension group than in the group with normal blood pressure, each being appreciably higher than in normal young subjects (Table I, Fig. 1). Beginning with the hands (Area 7), however, and continuing to the lower part of the body and the feet (Areas 7 to 11, inclusive), the relationship of the first two groups is reversed: in these areas the temperatures in the group with hypertension are cooler than in the normal blood pressure group. As compared with normal young subjects, the group of older subjects with normal blood pressure, except for the shin (Area 10), show higher temperatures. On the other hand, in the hypertension group the temperatures are lower than normal except in the hands (Area 7), where it is the same, and in the upper thigh (Area 8) where it is higher. The averages for the normal blood pressure group and hypertension group are higher than the averages for the normal young group for all areas except 9 and 10, namely the lower thigh and shin.

Blood Pressure.—The average of the blood pressure for the older subjects with normal blood pressure was 124/73, and 194/117 for the hypertension group, the average for the two combined groups being 156/98, as compared with 105/71 for the group of normal young men (Table I, Fig. 1).

Heart Rate.—The average heart rate for the older group with normal blood pressure was 65 per minute; for the hypertension group slightly higher, 77 per minute; and for both groups 72 per minute (Table I, Fig. 1). These are to be compared with the rate of 61 per minute in the group of normal young men.

Basal Metabolic Rate.—The basal metabolic rate was essentially the same for the normal blood pressure and hypertension group, namely +7 per cent and +9 per cent, respectively, as compared with –5 per cent for the group of normal young men (Table I, Fig. 1).

DISCUSSION

It appears, therefore, from observations made on these patients that there are certain differences in the peripheral circulation in older men as compared with normal young men. This is the case not only in those older men with

normal blood pressure but also in those with hypertension. In only one of the patients (L. M., No. 255998, Table I) in this study were there signs or symptoms of occlusive peripheral vascular disease. In the normal young subjects already reported[1] it was found that more blood was allotted to the periphery when the environmental temperature was 27° C., than at a lower temperature of 25° C.

The data relating to this older age group have been subjected to statistical analysis. On comparison of the hypertension group with the normal blood pressure group none of the differences were significant when the test of twice the standard deviation was applied; but there was a trend toward decrease in peripheral blood flow, increase in rectal temperature, and decrease in average weighted skin temperature, with increase in temperature of the upper parts of the body and decrease in temperature of the lower parts of the body.

When the older people with normal blood pressure are compared with young normal individuals, again the differences are not statistically significant. The peripheral blood flows are the same. The trend is for the rectal and average weighted skin temperature and the temperature of all the areas of the body to be increased in older people.

Again in older people with hypertension as compared with young normal subjects the differences are not significant, but there is a trend toward decrease in peripheral blood flow, an increase in rectal (all over 37° C. except one subject), and in average weighted skin temperature, and an increase in temperature of the upper part of the body and a decrease in the lower part.

When the whole old age group, including those with hypertension as well as those with a normal blood pressure, are compared with normal subjects, no statistically significant differences are revealed; but again the trend is toward a decrease in peripheral blood flow, a rise in the rectal and the average weighted skin temperatures, and a rise in temperature of the upper part of the body and a decrease in the lower part.

How can these data be fitted together? There is a trend toward decrease in peripheral blood flow when there is hypertension, with a rise in rectal and a decrease in average weighted skin temperature, both as compared to normal young subjects and to older subjects with normal blood pressure. Also it would appear to be more than chance that the temperature of the upper part of the body is warmer and that of the lower part is cooler in these hypertensive subjects than in those subjects in the same age group with normal blood pressure, a pattern which is similar to that exhibited by hypertensive patients in the earlier age group.[10]

SUMMARY

The peripheral blood flow and skin and rectal temperatures have been measured in 25 male patients from 38 to 77 years of age, that is to say in patients in the older age group. In 12 subjects there were clinical signs of vascular damage without hypertension, and in 13 there was also hypertension. In only one subject was there evidence of occlusive peripheral vascular disease. The results in these patients have been compared with those in normal young male

subjects. The peripheral blood flow was measured by a modification of the method of Hardy and Soderstrom. The following facts emerged:

1. The average peripheral blood flow at 27° C. (room temperature) is in the same range in older individuals with normal blood pressure, 73 c.c. per square meter of body surface per minute, as in younger male subjects, but is lower, namely 55 c.c. per square meter of body surface per minute in those with hypertension, and approaches the value recorded for normal young subjects at the cooler environmental temperature of 25° C.

2. The rectal temperature is higher in older people than in the young normal group (36.79° C.) and was slightly higher in the hypertension group (37.32° C.) than in the normal blood pressure group (36.95° C.).

3. The average weighted skin temperature was higher in both the normal blood pressure group (33.99° C.) and the hypertension group (33.92° C.) than in younger subjects (33.74° C.).

4. The skin temperatures of the individual areas of the body surface are warmer in the older patients with normal blood pressure than in younger individuals, except in one area, namely the shins (Area 10), where the temperature is lower in the older group. On the other hand patients with hypertension in the older age group have a warmer skin temperature in the upper part of the body, and a cooler temperature in the lower part of the body than do young normal subjects. The inference is that the peripheral blood flow to the feet is reduced, since their temperature is lower, and that the blood flow to the upper part of the body is increased, since its temperature is warmer. The reduction in peripheral blood flow in the lower part of the body is apparently greater than the increase in the upper part of the body so that the net result is an average peripheral blood flow for the whole body which is less than the value in normal young males at the same room temperature. In short, it is comparable to the constriction observed in normal young subjects in an environment of 25° C.

5. Patients with hypertension in this older age group show the same trends, but to a lesser extent, as are shown by patients with hypertension in the earlier decades.

REFERENCES

1. Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow Under Basal Conditions in Normal Male Subjects in the Third Decade, AM. HEART J. 26: 67, 1943.
2. Hardy, J. D., and Soderstrom, G. F.: Heat Loss From the Nude Body and Peripheral Blood Flow at Temperatures of 22° C. to 35° C., J. Nutrition 16: 493, 1938.
3. Stewart, H. J., and Jack, N. B.: The Effect of Aminophyllin on Peripheral Blood Flow, AM. HEART J. 20: 205, 1940.
4. Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow in Hyperthyroidism, AM. HEART J. 20: 715, 1940.
5. Stewart, H. J., and Evans, W. F.: Peripheral Blood Flow in Myxedema, Arch. Int. Med. 69: 808, 1942.
6. Hardy, J. D., and Soderstrom, G. F.: An Improved Apparatus for Measuring Surface and Body Temperature Rev. Scient. Instruments 8: 418, 1937.
7. Roth, P.: Modification of Apparatus and Improved Technique Adaptable to the Benedict Type of Respiration Apparatus, Boston M. & S. J. 186: 457, 1922.
8. Boothby, W. M., Berkson, J., and Dunn, H. L.: Studies of the Energy of Metabolism of Normal Individuals: A Standard for Basal Metabolism With a Nomogram for Clinical Application, Am. J. Physiol. 116: 468, 1936.
9. DuBois, D., and DuBois, E. F.: A Formula to Estimate Approximate Surface Area if Height and Weight Be Known, Arch. Int. Med. 17: 863, 1916.
10. Stewart, H. J., Evans, W. F., Haskell, H. S., and Brown, H.: The Peripheral Blood Flow, Rectal and Skin Temperatures in Hypertension. In press, AM. HEART J.

INTERATRIAL AND SINOATRIAL BLOCK, WITH AN ILLUSTRATIVE CASE

GEORGE M. DECHERD, JR., M.D., ARTHUR RUSKIN, M.D., AND
PAUL BRINDLEY, M.D.
GALVESTON, TEXAS

ALTHOUGH atrioventricular conduction disturbances are common and have been widely studied, the subject needs further investigation. Block between the two atria is rare, and little attention has been paid to it either experimentally or clinically. That it may occur has been recognized for many years, and a few undoubted clinical examples have been recorded.

If the pacemaker of the heart resides in the S-A node, the excitation wave should first pass to the adjacent right atrium before reaching the left, whether the wave spreads like "fluid poured upon a flat surface,"[1] or through functionally differentiated pathways in the muscle bands. The existence of an interval between contraction of the two atria was first recognized by Chauveau[2] in the horse, and later by Hering[3] in the dying hearts of smaller laboratory animals. This observation was confirmed by Frederieq,[4] Schmidt-Nielsen,[5] and Stassen.[6] This interval was measured electrically by Garten,[7] who set it at 0.0128 to 0.0139 second, apparently on the basis of experimental work done by Erfmann[8] and by Schneiders.[9] In 1916 Bachmann,[10] using a mechanical method, obtained a similar average, 0.013 second.

Dissociation between the two atria, either partial or complete, was first recorded in 1900 by Hering,[3] who also first emphasized that poor nutrition of the myocardium of the dying heart predisposed to block. Frederieq[4] divided the two atria of hearts perfused by the Langendorff method and noted the development of independent rhythms in the two parts. Later studies[11, 12] on hearts in situ supported these earlier experiments. Similar results were obtained by Bachmann,[10] Condorelli,[13] and Scherf and Siedek.[14]

Although Keith and Flack[15] and Thorel[16] thought that there were differentiated anatomic connections between the S-A node and the A-V node, their view has never been substantiated. The presence of functionally specialized conducting pathways within the atrial muscle bands was first postulated by Eyster and Meek,[17] who believed that they had demonstrated the existence of a special path from the S-A to the A-V node; later they[18] offered additional evidence in support of this theory in order to refute the criticism of Lewis and his associates.[19] Rothberger and Scherf[20] found that by tying one or both of two muscle bands, the first passing from the upper part of the S-A node to the left atrium, the second from the lower part of the S-A node along the Torus Lowerii through

From the Departments of Medicine and Pathology, University of Texas School of Medicine, and the Heart Station of the John Sealy Hospital, Galveston, Texas.
Received for publication July 3, 1945.

the interatrial septum to the A-V node, it was possible to interrupt the conduction of the sinus impulse to the ventricle and so to produce A-V nodal rhythm. When both pathways were broken, they assumed that the spread of the sinus impulse was through numerous secondary pathways to the atria and A-V node. Condorelli[21] listed eight separate connections between the S-A and A-V nodes, the most direct of which were the two tied by Rothberger and Scherf and a third originating in the middle of the S-A node and running into the interatrial septum. He stated that all fibers going to the A-V node united at one place in the lower part of the interatrial septum, between the coronary sinus and the fossa ovalis. If these pathways actually exist, one important implication of their presence would be the possibility suggested by Condorelli,[21] that their integrity, associated with impairment of fibers from the S-A node to the atrial muscle, might lead to shortening of the A-V conduction time as measured by the P-R interval.

Experimental evidence for the existence of a special pathway between the two atria was adduced by Erfmann.[8] Better known is the work of Bachmann,[10] who described the interatrial bundle (Bachmann's bundle) as follows: "In a dog's heart of average size the right extremity of the band originates about 5 mm. to the mesial side of the auriculocaval angle and in a direct line with it. This extremity of the band is immediately back of the aorta and spreads in a fan-like manner onto the mesial (right) auricular wall and the root of the superior vena cava. From this origin the band sweeps in an almost straight line to the base of the left auricular appendage but, so far as superficial appearance indicates, its fibers can be traced to near the tip of the left appendage. The band is thinnest near its origin on the right side where it has an angular appearance. It then broadens gradually as it passes to the left auricle. The band is slightly concave from right to left, the concavity being directed upward. It has a length of about 20 mm." Clamping this muscle band led to a prolongation of the interval between contraction of the two atria from a normal average of 0.013 second to an average of 0.05 second; in one instance the interval was as great as 0.98 second. Rothberger and Scherf[20] found that clamping this region produced various changes in the form of the P waves and an increase in the interatrial interval. They also observed a small artery which supplied this area. The origin and course of this artery was more carefully ascertained by Condorelli,[13] who succeeded in tying it in the experimental animal.

In the human heart, Spalteholz[22] designated this vessel as the *ramus atrialis sinister anterior*. Condorelli found that in the dog heart it might arise from the main left coronary artery or from the initial segments of either the anterior descending or circumflex branches. The latter origin was more common. Diagrams in Condorelli's paper show the artery clearly; it is also shown in Schlesinger's diagram, reproduced from Spalteholz. In several instances Schlesinger's[23] x-ray photographs show the vessel and it may also be identified in Gross' illustrations.[24] One illustration in a textbook of anatomy[25] shows the origin of this vessel. Shortly after its origin the artery sends an auricular branch to the left auricular appendage. The vessel then passes up and to the right, along the path of Bachmann's bundle, terminating in small twigs to the wall of the su-

perior vena cava near the sinoatrial node. This latter region is also supplied by the ramus atrialis dexter anterior, which arises from the first part of the right coronary artery.

Condorelli[13] found that ligature of the left anterior atrial artery produced changes in the P wave and in the sequence of atrial contraction which were similar to those produced by clamping or tying Bachmann's bundle. In two instances fibrillation was present in the left atrium, while a sinus rhythm, conducted to the ventricles, persisted in the right atrium. Analogous dissociation was produced by tying the anterior descending coronary artery near its origin from the left coronary artery, and in one animal interatrial block was produced, beginning with two-to-one and later progressing to complete block, in which sinus rhythm was seen in the right atrium, while there was complete standstill of the left atrium. Similar results were obtained by Scherf and Siedek[14] in poorly perfused Langendorff hearts and in hearts in situ whose interatrial artery had been tied. Condorelli and Scherf and Siedek emphasize the importance of an intact blood supply in maintaining normal relationships in the contraction of the two atria.

Clinical examples of interatrial dissociation are relatively few. The first case was recorded by Schrumpf,[26] whose patient was a 37-year-old man with rheumatic mitral stenosis and aortic insufficiency. During an episode of acute heart failure, he was given digitalis in toxic amounts. Electrocardiograms taken at this time showed two sets of P waves: P_1 with a rate of 64 per minute which was conducted to the ventricles with a P-R interval of 0.20 second, and P_2 with an independent rhythm and a rate of 109 per minute, which was not conducted to the ventricles. P_2 disappeared after three days, possibly because the digitalis was withdrawn. Schrumpf's assumption that these two independent series of P waves were due to two active S-A nodes has not been generally accepted.

Scherf and Siedek[14] have reported another case of partial interatrial block in a patient with an acute coronary thrombosis, which at necropsy was found to be in the left coronary artery just before its bifurcation into the circumflex and anterior descending branches. Complete A-V block was present, and the interatrial conduction time varied between 0.24 and 0.40 second. Although Scherf and Siedek made no mention of the interatrial artery, its usual origin is just distal to the occluded area, and presumably the supply of blood to the interatrial band was deficient.

Three more cases were reported by Bay and Adams.[27] Electrocardiograms of the first patient, a 22-year-old man with acute rheumatic fever, showed two independent sets of P waves: P_1 with a rate of 85 per minute, conducted normally to the ventricles; and P_2 with an average rate of 113 per minute. The second patient was a 9-year-old girl, and the third a 25-year-old man with chronic glomerulonephritis; electrocardiograms of both patients showed extra sets of complexes which may be atrial in origin, but whose appearance suggests strongly that they may be artifacts. Bay and Adams accepted Schrumpf's explanation for such findings and discussed extensively the possibility of anatomic and functional separation of the S-A node into two parts.

In 1935, Géraudel[28] recorded two instances of independent atrial rhythms in elderly patients with Cheyne-Stokes respiration. The P waves which were not conducted to the ventricles were more numerous during the polypneic phase of respiration. Duclos[29] reported one example of independent atrial rhythms in a 9-year-old girl who had no cardiovascular symptoms or other abnormal findings. Electrocardiograms showed two independent sets of P waves, one of which was regularly conducted to the ventricles. Tracings made on two subsequent occasions did not show these abnormalities. Dominguez and Bizzozero[30] found an example of double atrial rhythm in a 6-day-old infant; the P waves which were conducted to the ventricles occurred at a rate of 136 per minute; the independent P waves, of different contour and seen in both Lead I and III, had a rate of 110 per minute. They found only this single case among two hundred newborn infants examined electrocardiographically, although they quote Burghard and Wunnerlich[31] as having observed the so-called "double commande" in ten of thirty-two infants.

Lian and Golblin[32] have recorded a similar case. The patient, who was 71 years old, had had a coronary artery occlusion five years before. The second examination was done because of convulsive seizures. The electrocardiogram showed two-to-one A-V block, with bundle branch block, as well as deep Q waves in Leads II and III. Using the special lead designed to give large atrial complexes, from the manubrium to the fifth right intercostal space at the sternal border, Lian and Golblin recorded two series of P waves. One series, with a rate of 88 per minute, showed the two-to-one block; the other series, consisting of deeply negative waves, had a rate of 76 per minute and was independent of the first series. The authors point out that their curves, which were obtained from a patient with coronary artery occlusion, resemble those recorded by Scherf and Siedek in experimental interatrial block which was produced by clamping the small artery supplying the Bachmann bundle.

Hertz[33] also reported one case; the patient was a 17-year-old girl who had had a large goiter removed a year before because of tracheal compression. The electrocardiograms showed two sets of P waves, each occurring at about the same rate of 55 per minute, with one set conducted to the ventricles with a P-R interval of 0.15 second. It is not certain that the two sets are independent; there appears rather to have been a transient delay in interatrial conduction, with rapid return to normal.

Luisada[34] has reviewed the subject of both partial and complete interatrial dissociation, with particular reference to the work of his Italian colleagues. His own electrocardiograms were simultaneous records of an esophageal lead, for the left atrium, and a mouth-xiphoid lead, for the right atrium. He demonstrated delay in left atrial response, particularly in mitral stenosis, and showed several curves which he interpreted as representing flutter in the right atrium with fibrillation in the left. Delay in left atrial response in mitral stenosis was also described by Mahaim.[35] The widely notched P waves that he described are exaggerated examples of the notched P waves commonly seen where there is enlargement of the left atrium in mitral stenosis.

Several cases are on record which have been interpreted as dissociation of the atria, with longitudinal dissociation of the ventricles as well (Hoffmann,[36] Burghard and Wunnerlich,[31] Kerr and Sampson,[37] and Géraudel[38, 39]). Other cases have been thought to represent interatrial dissociation, but have subsequently received a different interpretation. The first such case was that of Wenckebach,[40] who also was the first to propose a clinical diagnosis of interatrial dissociation. Other similar cases have been reported by Roth,[41] Danielopolu and Proca,[42] Kure and Kaneko,[43] and Lombardini and Aviles.[44]

REPORT OF CASE

Our patient was a 36-year-old Negro woman, who entered the John Sealy Hospital on Oct. 9, 1944, because of severe nausea and vomiting of three weeks' duration. She had had severe headaches during the preceding three years, and blurring of vision had been marked for three days before admission. Her blood pressure was 222/170; the fundi showed marked hypertensive retinopathy, with papilledema. On October 10, the blood nonprotein nitrogen was 57 mg. per 100 c.c.; the creatinine 5.1 mg. per cent. These values rose gradually, and, on November 10, the nonprotein nitrogen was 259 mg. per cent. Venous pressure and circulation time were normal. The gastrointestinal symptoms persisted, and in addition the patient suffered several attacks of severe epigastric and substernal pain. She became stuporous; muscular twitching occurred repeatedly; and on November 4 she had a generalized convulsion. On November 13 the heart was first noted to be irregular, with apparent dropping of every third beat. The patient died on Nov. 15, 1944.

The electrocardiograms taken on October 10 showed changes consistent with hypertensive heart disease (Fig. 1). Surprisingly favorable changes took place during the next few weeks, so that, on November 7, the T waves in Leads I and II, which were previously negative, had become positive. On November 13 the bigeminy observed clinically was thought to be due to atrial premature beats. The T waves in Leads I and II were high, the S-T segments were slightly elevated and the T waves in Lead CF_2 had become negative. These changes were associated with clinical evidences of uremic pericarditis.

The curve taken on November 14 is reproduced more extensively (Fig. 2), particularly Lead CF_2, since in this curve the atrial complexes are best seen. Preceding the first of each pair of ventricular complexes may be seen two atrial deflections; the first is chiefly positive and is followed, after an interval of 0.28 second by the second deflection, which, though diphasic, is chiefly negative. The second beat of the pair of ventricular complexes is preceded by the same atrial deflections, which, however, are much closer together. In every instance the QRS complex follows the second negative atrial deflection after a uniform P-R interval of 0.18 second.

At necropsy there were 600 c.c. of fluid in the right pleural space and 850 c.c. in the left. The abdominal cavity contained 1,200 c.c. of clear straw-colored transudate. The pericardial sac contained 55 c.c. of opalescent fluid, and there was a thin fibrinous exudate on the pericardial surface. The heart weighed 650 grams; there was moderate atherosclerosis in the coronary arteries, but no occlusion. Early lobular pneumonia was present in the lungs, with edema and chronic passive congestion. There were ulcers in the esophagus, stomach, intestine, and colon. The right kidney weighed 200 grams, the left, 85 grams. The stripped surfaces were finely granular.

The pathologic diagnosis included arteriolar nephrosclerosis, cardiac hypertrophy, fibrinous pericarditis, ulceration of the gastrointestinal tract, pulmonary edema and early lobular pneumonia, hydrothorax, acute edema of the brain, pyelitis, and fibromyomas of the uterus.

Careful dissection of the coronary arteries showed a branch arising a few millimeters from the origin of the left circumflex artery and supplying the left auricular appendage and the area of Bachmann's bundle. This small vessel could be traced across the atria to the region of the S-A node and the wall of the superior vena cava. Its course was perfectly

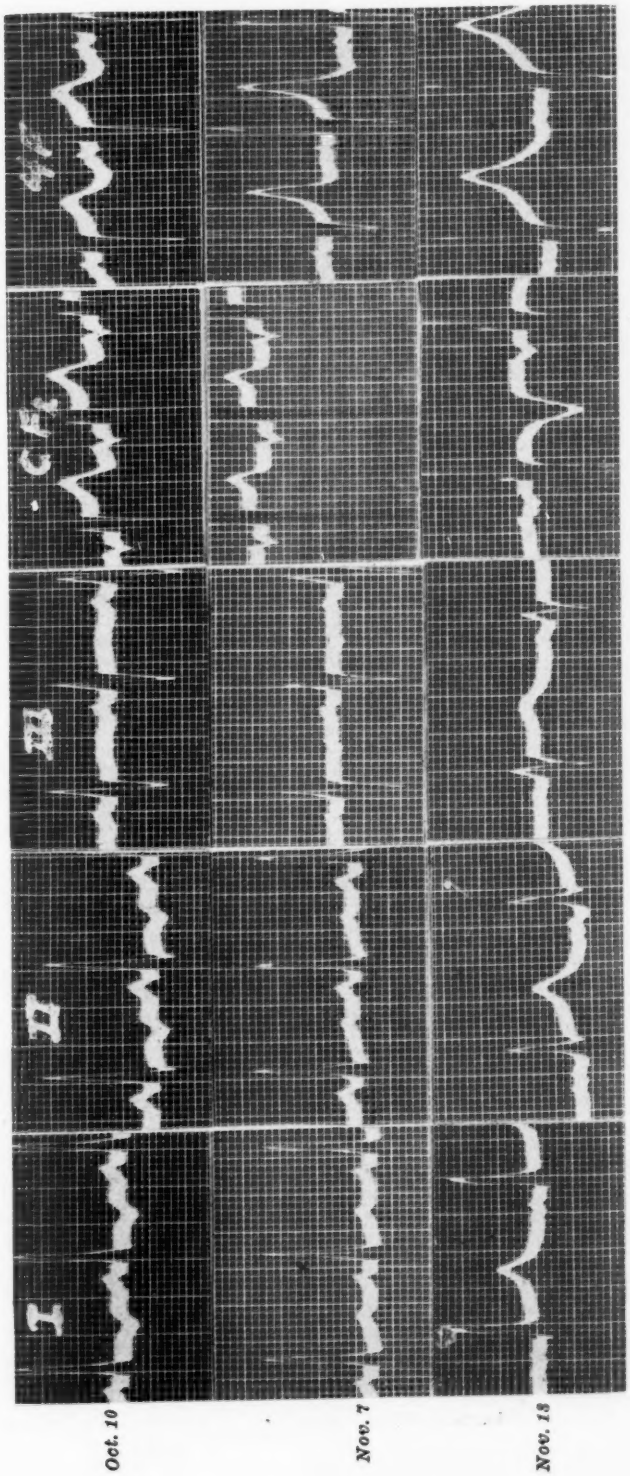


Fig. 1.—Leads I, II, III, CF_5, and IVF made on Oct. 10, Nov. 7, and Nov. 13, 1944. Note especially Lead CF_5 on the last date.

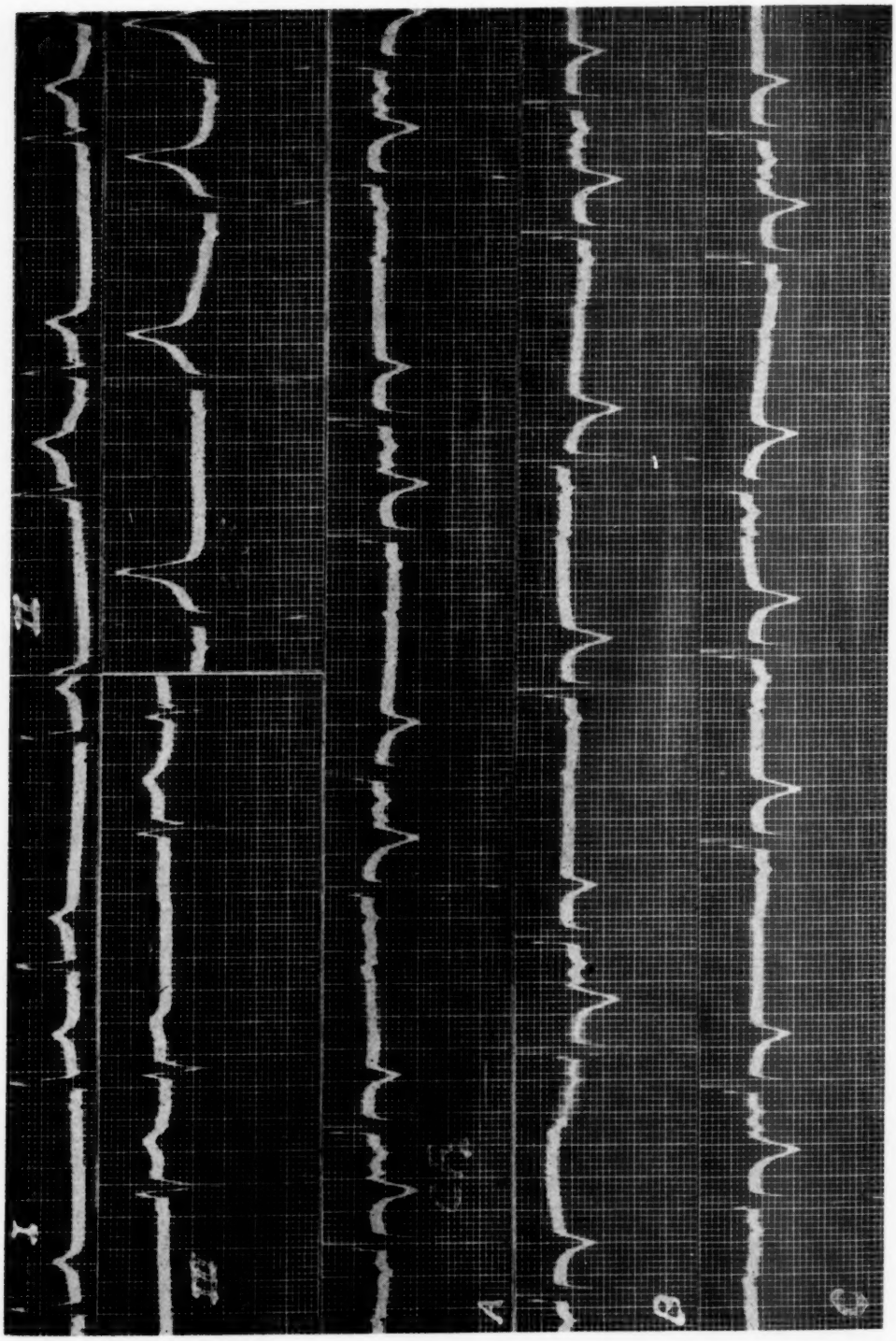


Fig. 2.—The three limb leads and Lead IVF on Nov. 14, 1944, are shown in the first two lines. The last three lines, *A*, *B*, and *C*, are all Lead CFs; *B* and *C* are continuous strips. See text and Fig. 3 for comment.

analogous to that of the vessel described in the dog heart by Condorelli.[21] Multiple sections taken along the course of this vessel showed no evidence of obstruction. The only histologic abnormalities were those due to a moderate uremic pericarditis; the muscle fibers were hypertrophied but otherwise normal.

The large branch of the right coronary artery which supplies the region of the S-A node was likewise carefully dissected and examined. Grossly there was no obstruction, and sections of this vessel showed only a slight intimal fibrosis at one point which decreased the size of the lumen only slightly.

COMMENT

The electrocardiograms of this patient show partial block between the two atria, with loss of normal synchronous excitation. In the absence of any demonstrable anatomic disruption of intra- and interatrial communications, this asynchrony must be presumed to be on a functional basis.

The two complexes of atrial origin cannot with certainty be identified with right or left atrial activity. Since the second complex is constantly related to the QRS complex, it is most likely due to right atrial excitation; if this is true, the first atrial complex must, then, be due to left atrial excitation. The converse interpretation is not impossible, since ventricular response to left rather than to right atrial activity was demonstrated experimentally by Scherf and Siedek.[14] This point cannot be determined from the electrocardiogram alone. A simultaneous jugular pulse tracing would have enabled us to identify the response of the right atrium, but unfortunately the patient died before we realized the desirability of such a record.

The wide separation of the two atrial complexes which precede the first of each pair of ventricular beats suggests a partial interatrial block. The atrial complexes which precede each second ventricular beat adjoin each other closely, though each portion can be identified. The same phenomena were present in the electrocardiogram of November 13 (Fig. 1, Lead CF_2), but they were so inconspicuous that they were overlooked at that time, and the bigeminy was interpreted to be due to atrial premature beats. The closer approximation of the atrial complexes preceding the second of each pair of ventricular complexes may be evidence of facilitation of conduction between the two atria, although the explanation which follows seems more logical.

Partial A-V block with dropped beats may be of two kinds: Type I, the Wenckebach type, in which the P-R interval gradually increases until an atrial complex is blocked; or Type II, the Mobitz type, in which the P-R interval is uniform until sudden blocking of an atrial complex takes place. Type I is commonly caused by the action of digitalis, while Type II is more likely to be the result of disease of the conduction pathways. The same concepts may be extended to S-A block.

The common variety of S-A nodal arrest or block needs little comment, since it has been adequately discussed.[45] The occurrence of the Wenckebach phenomenon, with progressively greater delay in conduction between the S-A node and the atrial tissues, has rarely been commented upon, though it has long been known to exist. In 1908, Rihl[46] described such a physiologic mechanism quite clearly, basing his reasoning on polygraphic records. Lewis[1] showed diagram-

matically an instance of S-A block in which the impulses from the S-A node reached the atria "after a delay which varies according to the duration of the preceding periods of rest." In an electrocardiographic study of one hundred children with scarlet fever, Wickström[47] observed three instances of this variety of S-A block. A similar example was described and analyzed by Lühr[48]; the patient, an elderly man who had received large amounts of digitalis during the treatment of congestive heart failure, showed a varying four-to-three, five-to-four, and three-to-two block. Blumberger[49] discussed a single example of each type of S-A block, and later[50] reported a second instance of the Wenckebach type. Vedoya et al.[51] reported four examples of S-A block, in three of which the sinoatrial conduction time increased progressively. Katz[52] illustrated this phenomenon in his recent text.

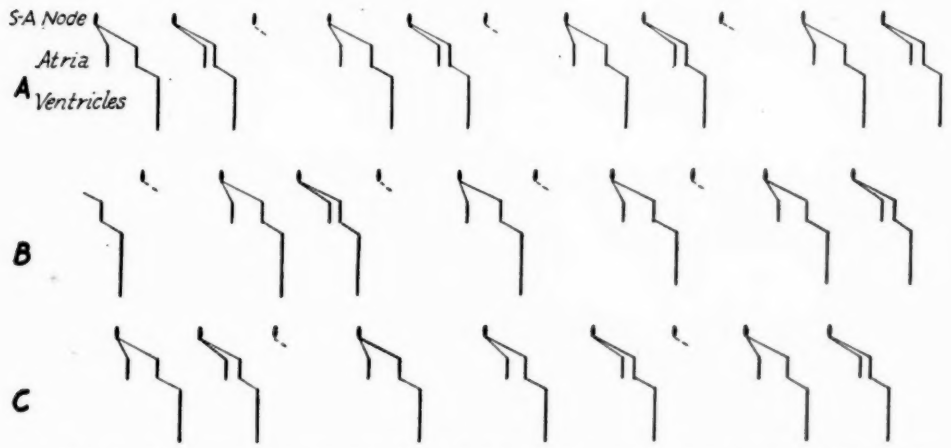


Fig. 3.—Diagrammatic representation of intracardiac conduction corresponding to the complexes shown in Fig. 2, *A*, *B*, and *C*. The usual mechanism is a three-to-two sinoatrial block, with the Wenckebach type of progressively increasing sinoatrial conduction time to the first atrial complex, and uniform conduction time to the second atrial complex until block appears. In line *B* there are two cycles of two-to-one block, and in line *C* a single cycle of four-to-three block.

It is probable that true complete block between the two atria, or between one atrium and the S-A node, exists in those reported cases of interatrial block that have shown two independent sets of P waves. On the other hand, what seems to be partial interatrial block may actually be partial sinoatrial block; Hertz' case[33] may be an example of this.

Careful measurements of the atrial complexes in our tracings show that the second negative complex (Fig. 2, Lead CF_2) occurs at a fairly regular rate of about 80 per minute (interval about 0.75 second), with each third beat usually dropped. This implies a three-to-two block between the S-A node and the atria. The same mechanism may also be assumed to explain the variable position of the first atrial complex of each pair; this concept is shown diagrammatically in Fig. 3. In this figure conduction from the S-A node to the two atria is represented by slanting lines, in the conventional manner, with the length of the lines and their angles roughly proportional to the conduction time.

The time at which S-A nodal discharge occurs must be, of course, entirely hypothetical. The conduction time from the S-A node to the (left?) atrium is shown to progressively increase, a behavior which is analogous to the Wenckebach type of A-V block. The conduction time to the (right?) atrium is uniform; A-V conduction time is constant until the block occurs. In each instance there is usually a three-to-two block; for a short period, Fig. 2, *B*, and 3, there is a two-to-one block; in the last line, Fig. 2, *C*, and 3, where there is transient slowing of the S-A nodal rhythm, the block is four-to-three. Thus, the assumption that the Wenckebach type of block is present between the S-A node and one atrium, and the Mobitz type of block between the node and the other atrium, logically explains the varying intervals of time between the two individual atrial complexes.

It is possible to measure tentatively the relative conduction times from the S-A node to the two atria. If the S-A nodal discharge is assumed to occur 0.01 second before the first of the two P waves, and if the conduction to the second atrial complex is uniform, increasing sinoatrial conduction times may be deduced for the three unpaired complexes of Fig. 2, *C*. These periods are 0.01, 0.11, and 0.17 second, respectively. Thus the greatest increase in conduction time is found in the second cycle of the group, a feature that is characteristic of the Wenckebach type of A-V block.

SUMMARY

Sinoatrial block of two types has been described; (1) with progressive prolongation of sinoatrial conduction time leading to a dropped beat; and (2) dropped beats without such preceding conduction changes. These are strictly analogous to the Wenckebach and the Mobitz types of atrioventricular block. The literature on this subject has been surveyed, together with available information on the postulated anatomic and functional pathways of inter- and intra-atrial conduction.

We have postulated that, in the present case, both varieties of sinoatrial block coexist, thus explaining the variable distance between the two types of P waves. Such a hypothesis also requires the assumption of functional pathways between the S-A node and the two atria, with dissociation of the two atria, and with partial dissimilar block between each atrium and the S-A node. Although interatrial dissociation, both partial and complete, and each variety of sinoatrial block have been previously described, so far as we have been able to learn, their coexistence has not been previously noted.

REFERENCES

1. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, 1925, Shaw and Sons.
2. Chauveau, A.: Quoted by Bachman.[10]
3. Hering, H. D.: Zur experimentellen Analyse der Unregelmässigkeiten des Herzschlages, Arch. f. d. ges. Physiol. **82**: 1, 1900.
4. Frederieq, L.: Sur la pulsation de la veine cava superieure et des oreilettes du coeur chez le chien, Acad. roy. de Belg., Bull. de la Cl. d. sc. **3**: 126, 1901.
5. Schmidt-Nielsen, S.: Le pretendu synchronisme de la systole des deux oreillettes, Arch. internat. de physiol. **4**: 417, 1907.

6. Stassen, M.: De l'ordre de succession des differentes phases de la pulsation cardiaque chez le chien, Arch. internat. de Physiol. 5: 60, 1907.
7. Garten, S.: Über die Verwendung der Differential-elektroden am Säugetierherzen, Skandinav. Arch. f. Physiol. 29: 114, 1913.
8. Erfmann, W.: Ein Beitrag zur Kenntnis der Fortleitung der Erregungsvorganges im Warmblüterherzen, Ztschr. f. Biol. 61: 155, 1913.
9. Schneiders, M.: Ein Beitrag zur Kenntnis der Fortleitung der Erregungsvorganges im künstlich durchbluteten Zäugetierherzen, Ztschr. f. Biol. 65: 465, 1915.
10. Bachmann, G.: The Inter-Auricular Time Interval, Am. J. Physiol. 41: 309, 1916.
11. Fredericq, L.: La pulsation du coeur du chien, Arch. internat. de Physiol. 4: 60, 1906.
12. Fredericq, L. Isolement de l'oreillette droite par écrasement sur le coeur vivant du chien, Arch. internat. de Physiol. 12: 109, 1912.
13. Condorelli, L.: Experimentelle Untersuchungen über die interaurikuläre Reizleitung, Ztschr. f. d. ges. exper. Med. 68: 516, 1929.
14. Scherf, D., and Siedek, H.: Über Block zwischen beiden Vorhöfen, Ztschr. f. klin. Med. 127: 77, 1934.
15. Keith, A., and Flack, M.: The Form and Nature of the Muscular Connections Between the Primary Divisions of the Vertebrate Heart, J. Anat. & Physiol. 41: 172, 1907.
16. Thorel, C.: Vorläufige Mitteilung über eine besondere Muskelverbindung zwischen der Cava superior and dem Hisschen Bundel, München. med. Wchnschr. 56: 2159, 1909.
17. Eyster, J. A. E., and Meek, W. J.: Experiments on the Origin and Propagation of the Impulse in the Heart. I. The Point of Primary Negativity to Other Regions, Heart 5: 119, 1913-1914.
18. Eyster, J. A. E., and Meek, W. J.: Experiments on the Origin and Conduction of the Impulse in the Heart. *8.* The Permanent Rhythm Following Destruction of the Sino-Auricular Node, Am. J. Physiol. 61: 117, 1922; Sino-Ventricular Conduction, ibid. 61: 130, 1922.
19. Lewis, T., Meakins, J., and White, P. D.: The Excitatory Process in the Dog's Heart, Phil. Tr. London, Ser. B. 205: 375, 1914.
20. Rothberger, C. J., and Scherf, D.: Zur Kenntnis der Erregungsausbreitung vom Sinusknoten auf den Vorhof, Ztschr. f. d. ges. exper. Med. 53: 792, 1927.
21. Condorelli, L.: Über die Bahnen der Reizleitung vom Keith-Flackschen Knoten zu den Vorhöfen, Ztschr. f. d. ges. exper. Med. 68: 493, 1929.
22. Spalteholz, W.: Die Arterien der Herzwand, S. Heizel, Leipzig, 1924.
23. Schlesinger, M. J.: An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, AM. HEART J. 15: 528, 1938.
24. Gross, L.: The Blood Supply to the Heart in Its Anatomical and Clinical Aspects, New York, 1921, Paul B. Hoeber.
25. Schaeffer, J. P.: Morris' Human Anatomy, ed. 10, Philadelphia, 1942, The Blakiston Co., Fig. 484, p. 597; dissection by Dr. R. F. Blount.
26. Schrumpf, P.: De l'interference de deux rythmes sinusaux; preuve du dualisme du nodule de Keith, Arch. d. mal. du coeur 13: 168, 1920.
27. Bay, E. B., and Adams, W.: Possible Intranodal Block. A Report of Cases, AM. HEART J. 7: 759, 1932.
28. Géraudel, E.: La double commande; étude des tracés où coexistent deux commandes indépendantes, l'une auriculoventriculaire, l'autre auriculaire, Arch. d. mal. du coeur 28: 121, 1935.
29. Duclos, F.: Un caso de "doble mando auricular," Arch. cardiol. y hemat. 16: 175, 1935.
30. Dominguez, C., and Bizzozero, R. C.: Double commande auriculaire, Arch. d. mal. du coeur 30: 820, 1937.
31. Burghard, E., and Wunnerlich, A.: Das Elektrokardiogramm des Säuglings, des Neugeborenen, und des Frühgeborenen, Ztschr. f. Kinderh. 45: 56, 1927.
32. Lian, C., and Golblin, V.: Un cas de double rythme auriculaire par dissociation interauriculaire, Arch. d. mal. du coeur 31: 52, 1938.
33. Hertz, J.: A Case of Double Auricular Action With Onesided Block, Acta med. Scandinav. 101: 409, 1939.
34. Luisada, A.: A Review of Advances in the Study of Auricular Disorders, J. Lab. & Clin. Med. 25: 1146, 1940.
35. Mahaim, I.: De l'anévrisme primitif de l'oreillette gauche, troubles particuliers du rythme cardiaque; la dissociation inter-auriculaire, Ann. d. méd. 21: 380, 1927.
36. Hoffmann, A.: Die Elektrographie als Untersuchungsmethode des Herzens und ihre Ergebnisse, Bergmann, Wiesbaden, 1914; quoted by Géraudel[38] and Kerr and Sampson.[37]
37. Kerr, W. J., and Sampson, J. J.: Functional Longitudinal Block in the Human Heart. A Probable Case With Unusual Arrhythmia, AM. HEART J. 7: 574, 1932.
38. Géraudel, E.: La double commande integrale, Arch. d. mal. du coeur 27: 524, 1934.

39. Géraudel, E.: La theorie vestibulaire du mécanisme cardiaque, Presse med. **43**: 297, 1935.
40. Wenckebach, K. F.: Beiträge zur Kenntnis der menschlichen Herztätigkeit, Arch. f. Anat. u. Physiol. 297, 1906.
41. Roth, O.: Über isolierte linksseitige Vorhofs-tachysystolie, Ztschr. f. klin. Med. **80**: 351, 1914.
42. Danielopolu, D., and Proca, G. G.: Recherches sur le rythme atrioventriculaire chez l'homme, Arch. d. mal. du coeur **19**: 217, 1926.
43. Kure, K., and Kaneko, H.: Ein Fall von Dissoziation der beiden Vorhofskontraktionen mit dem Kammersystolenausfall, Klin. Wchnschr. **5**: 1523, 1926.
44. Lombardini, R. V., and Aviles, M. D.: La interferencia el doble comando y los ritmos parciales. Dos casos de flutter auricular parcial simultaneos con el ritmo sinual que por momentos interfieren sus estimulos, Rev. argent. de cardiol. **5**: 380, 1939.
45. Wallace, A. W., and Katz, L. N.: Sino-Auricular Block, Am. Heart J. **6**: 478, 1931.
46. Rihl, J.: Klinischer Beitrag zur Kenntnis der Überleitungsstörungen von der Bildungstätte der Ursprungsreize zum Vorhof, Deutsches Arch. f. klin. Med. **94**: 303, 1908.
47. Wickström, J.: Eine elektrokardiographische Untersuchung über das Herz beim Scharlach, Acta Paediat. (supp. 4) **14**: 1933.
48. Lühr, K.: Ein seltenes und wechselvolles Elektrokardiogramm, Deutsches Arch. f. klin. Med. **177**: 65, 1934.
49. Blumberger, K.: Die Unterscheidung zweier Typen von sinaurikulärem Block, Deutsche med. Wchnschr. **62**: 1377, 1936.
50. Blumberger, K.: Wenckebachsche Perioden, Ztschr. f. klin. Med. **131**: 500, 1937.
51. Vedoya, R., Gonzales Videla, J., and Aguiar, R.: Sino-Auricular Blocks, Rev. argent. de cardiol. **7**: 277, 1940-41.
52. Katz, L. N.: Electrocardiography, Philadelphia, 1941, Lea & Febiger.

Clinical Reports

SPONTANEOUS MEDIASTINAL EMPHYSEMA

A Case Report Demonstrating Electrocardiographic Changes

Major Oscar A. Palatucci, M.C., and
Lieutenant Colonel James E. Knighton, M.C.
Army of the United States

WITHIN a period of twelve months, three instances of mediastinal emphysema with and without pneumothorax came to our attention at an Army Station Hospital. The first was found in a soldier who some months previously had had a thoracotomy because of pulmonary abscess of the upper lobe of the left lung. Subcutaneous emphysema was present and was quite extensive. The second occurred during an attack of bronchial asthma in a patient with chronic asthma and was complicated further by left pneumothorax. The third example, which may properly be called spontaneous, in that no definite causative factor could be found, will be reported in detail.

We wish to add this case to the growing literature on this subject and, at the same time, to present an interesting electrocardiographic finding which we believe has not been demonstrated previously. Hamman[1] states that the electrocardiogram in mediastinal emphysema does at times show abnormalities, but that the changes are not marked. He has not observed the changes that we wish to report.

CASE REPORT

The patient, white, 40 years old, was a master sergeant with twenty-three years of Army service. He was hospitalized because of precordial pain. There was no history of familial or hereditary disease. Except for the usual childhood diseases, the patient had enjoyed perfect health. He had no serious illness or injury and had undergone no operation. On the day prior to hospitalization a sharp, stabbing pain which prevented deep inspiration had developed in the left lower side of the chest posteriorly. The pain gradually diminished and after seven hours ceased completely. The next morning the patient awoke feeling perfectly well. About 9:00 A.M., while at his desk, he was again seized with a severe pain in the left upper side of the chest and the tip of the left shoulder. The pain radiated to the left side of the neck and along the left costal margin. The pain was constant, was intensified by deep breathing, and was accompanied by profuse sweating. No other symptoms were present.

The patient was obviously in acute distress because of thoracic pain. The temperature was 97° F., the pulse rate 88 per minute, and the respirations 16 per minute. The blood pressure was 122/74. The patient was 73½ inches in height and weighed 150 pounds. Positive physical findings were present only in the anterior left side of the chest. In the supine position the heart sounds were barely audible. Adventitious sounds were present

Received for publication March 31, 1945.

but were limited to faint clicking noises, synchronous with systole, over the precordium and along the left sternal border. When the patient assumed the sitting position, there was a marked increase in the abnormal sounds, which then became the typical crunching, crackling, popping noises which have been described as characteristic of mediastinal emphysema. In addition, the heart sounds became much more clearly audible and seemed to be normal in tone and character.

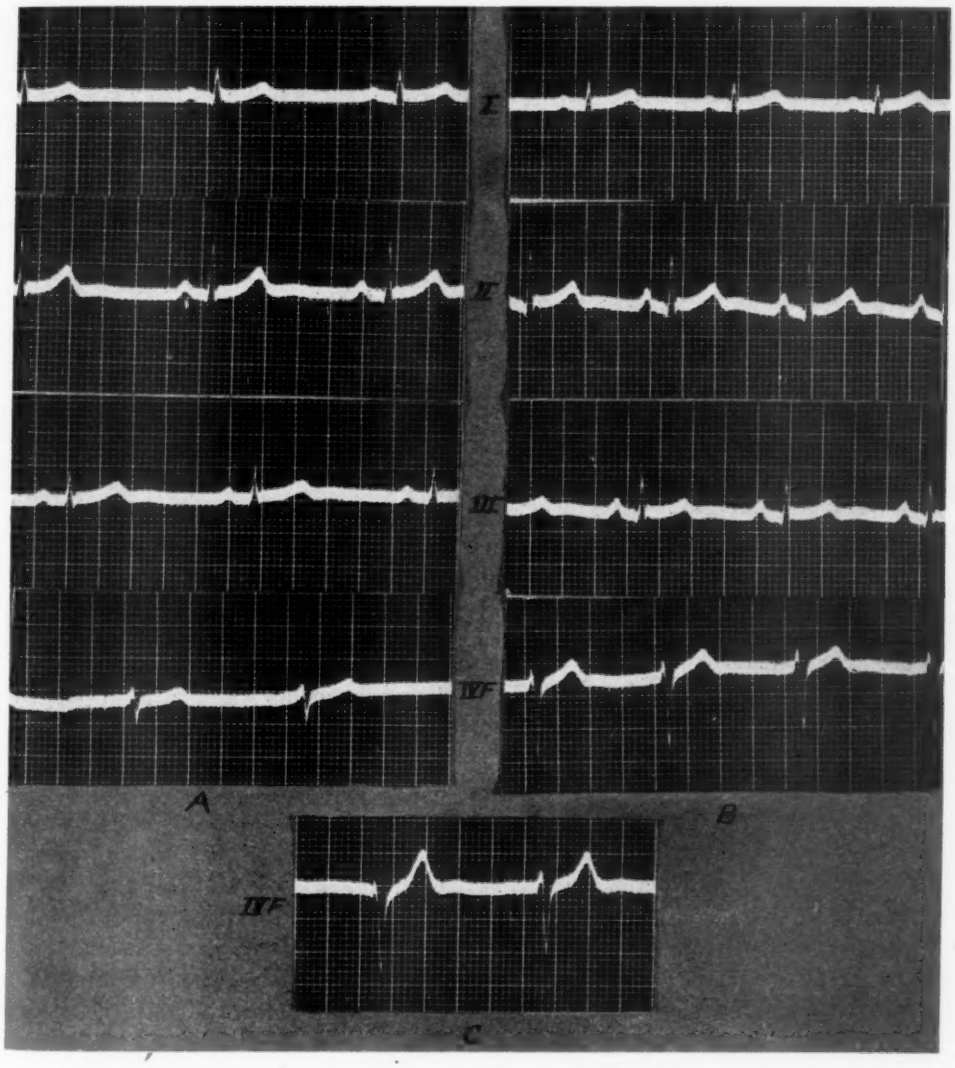


Fig. 1.—The tracings *A*, taken with the patient supine, and *B*, made in the sitting position, were obtained while mediastinal emphysema was present. The tracing marked *C* was made in the supine position after reabsorption of air from the mediastinum.

The laboratory reported no urinary abnormality, and the erythrocyte and leucocyte counts were well within normal limits. Roentgenographic examination of the chest in postero-anterior, lateral, and oblique projections revealed no evidence of pneumothorax or of air in the mediastinum. The heart was normal in size, shape, and position, and the lung fields were reported to be healthy. The electrocardiographic findings will be discussed later.

The pain subsided with bed rest and mild sedation. Treatment was entirely symptomatic, and all abnormal findings disappeared within nine days. The soldier then returned to duty, and when last seen, nine months later, reported that he had experienced no further difficulty.

An electrocardiogram was made on the third hospital day. Only the three standard limb leads were obtained, and these were normal except that the voltage was slightly lower than normal. On the sixth hospital day, electrocardiograms, including Lead IVF, were made with the patient both supine (Fig. 1, *A*) and sitting (Fig. 1, *B*). A comparison of these two tracings reveals practically no change in the limb leads. In the apical precordial leads, however, there are marked differences in voltage. In Lead IVF, taken with the patient supine, the voltage is definitely lower than normal, whereas in Lead IVF, made with the patient in the sitting position, the voltage is within normal limits. The total excursion of the QRS deflection of IVF taken supine measures less than 6 mm.; whereas in IVF taken in the upright (sitting) position the amplitude is 14 millimeters. The T waves present similar variations in voltage. On the ninth hospital day, when adventitious sounds could no longer be heard, a third tracing of Lead IVF was obtained with the patient supine (Fig. 1, *C*). This was practically identical with the tracing obtained three days previously with the patient upright. In an electrocardiogram made in the supine position nine months later, the limb leads did not differ from those shown in Fig. 1, *A* and *B*. The precordial lead of this later tracing was identical with the earlier precordial lead made in the supine position when physical signs were absent (Fig. 1, *C*). It was also identical with Lead IVF made in the sitting position when physical signs were present (Fig. 1, *B*). It does differ considerably from Lead IVF taken supine when the emphysema was present.

DISCUSSION

Hamman's original description of spontaneous mediastinal emphysema is contained in an article bearing the title "Remarks on the Diagnosis of Coronary Occlusion."[2] A few years previously, in a discussion entitled "Angina Pectoris," Wolferth and Wood[3] described an instance of pneumothorax with precordial knock occurring after severe exertion. Recognition of the pathognomonic auscultatory finding, Hamman's sign,[4] has done much to eliminate erroneous diagnoses, although mediastinal emphysema, when mild in degree and uncomplicated by either subcutaneous emphysema or pneumothorax, probably continues to go unrecognized.[5] Moreover, intrathoracic vascular accidents are still confused with this condition and must be differentiated therefrom.[6, 7] The first diagnosis in the case reported herein was coronary disease. This is readily understandable when one considers the rather sudden onset of precordial pain radiating to the left shoulder and side of the neck, the profuse perspiration and shocklike picture, and the very feeble faint heart sounds while the patient was in the supine position. The fact that x-ray examination failed to demonstrate air in the mediastinum or pleural cavities seemed to strengthen the original impression. However, the characteristic chest signs and the return of the normal heart tones when the patient assumed the upright position left no room for further doubt as to the correct diagnosis. It was the marked change in intensity of the heart sounds which change in posture which led to the taking of electrocardiograms in both the supine and sitting positions. The resultant wide discrepancy in voltage obtained in Lead IVF is clearly portrayed in Fig. 1.

The explanation which immediately occurred to us was a mechanical one. We thought that as the patient arose from the supine position the heart moved

anteriorly, this displaced the air in the anterior mediastinum and permitted the heart to come into contact with the anterior chest wall. This resulted in an accentuation of the crunching noises, and, as a result of the heart's being closer to the chest piece of the stethoscope, an intensification of the cardiac sounds. Conversely, when the patient reclined, the heart fell back, displacing air which had accumulated behind it, and allowed the air to return into the anterior mediastinum. This caused the heart sounds to become faint because a layer of air now separated the heart from the chest wall and stethoscope.

We believe the insulating effect of air in the anterior pericardial tissues is responsible for both the faintness of the heart sounds heard on auscultation and the low voltage in the electrocardiogram. It is known that the magnitude of the potential variations produced by the heartbeat at any point outside the heart itself diminishes rapidly as the distance from the epicardial surface increases.[8] The interposition of air between the heart and the precordial electrode would not only increase the distance separating the two, but would also further reduce the magnitude of the potential variations, since air itself is a poor conductor of electricity. Wilson[9] states that, in precordial tracings taken on patients with pneumopericardium produced after aspiration of fluid, the deflections are usually extremely small. Evidence to support the suggested mechanism of the changes observed in this case is found in the electrocardiogram obtained when all the mediastinal air had been reabsorbed, as determined by the disappearance of adventitious sounds and the return of the normal intensity of the heart tones with the patient supine. At this time Lead IVF (Fig. 1, *C*) was identical with Lead IVF obtained three days earlier with the patient in the upright position. The apical lead obtained nine months later with the patient in the supine position is also similar to the two mentioned previously.

This proposed explanation was submitted for comment to Dr. Frank N. Wilson, who graciously replied that with air between the precordial electrode and the heart one could probably expect findings similar to those observed in this case. Should it be found that other cases present the same, or similar, variations in physical and electrocardiographic findings with change in position of the patient, the changes we have described may prove to be of diagnostic importance, particularly in questionable cases in which pneumomediastinum is not demonstrable by roentgenography.

SUMMARY

1. A case of spontaneous mediastinal emphysema is reported.

2. Electrocardiographic changes not previously reported were observed. These changes are demonstrated.

3. The possible etiology of these changes is discussed.

4. Possible diagnostic value is ascribed to the findings which are described.

REFERENCES

1. Hamman, L.: Personal communication.
2. Hamman, L.: Remarks on the Diagnosis of Coronary Occlusion, Ann. Int. Med. 8: 417, 1934.

3. Wolferth, C. C., and Wood, F. C.: Angina Pectoris, M. Clin. North America 13: 947, 1930.
4. Hamman, L.: Spontaneous Mediastinal Emphysema, Bull. Johns Hopkins Hosp. 64: 1, 1939.
5. Macklin, Madge T., and Macklin, Charles C.: Malignant Interstitial Emphysema of the Lungs and Mediastinum as an Important Occult Complication in Many Respiratory Diseases and Other Conditions, Medicine 23: 281, 1944.
6. Cabot, R. C., and Adams, F. D.: Physical Diagnosis, ed. 13, Baltimore, 1942, Williams and Wilkins Co., p. 522.
7. Lintz, Robert M.: Spontaneous Mediastinal Emphysema, Arch. Int. Med. 71: 256, 1943.
8. Wilson, Frank N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., de Oliveria, R. M., Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, AM. HEART J. 27: 19, 1944.
9. Wilson, Frank N.: Personal communication.

PURE CONGENITAL PULMONARY STENOSIS

Case Report

Major Alexander N. Freed, M.C., and Captain Joseph Budnitz, M.C.

PULMONARY stenosis in the heart without additional congenital defects is a rare occurrence. In a clinical and postmortem analysis of 105 cases of congenital heart disease by Gibson and Clifton[1] only two cases were found with uncomplicated pulmonary stenosis. The 1,000 cases of congenital heart disease analyzed by Maude Abbott[2] include only nine such cases. The bibliography of these cases was recently compiled by Bauer and Astbury[3] who noted that the ages at the time of death were 10½ to 45 years with an average age of 22.8 years. Congenital pulmonary stenoses which allowed an average life expectancy of nearly 23 years were obviously not as marked or as severe in degree as the one to be reported here in which the opening in the stenotic valve was 2 mm. and the subject died of right-sided heart failure at the age of 11 months.

CASE REPORT

Mrs. G. consulted one of us (A. N. F.) about her 8-month-old daughter because, ever since birth, the following symptoms had been noted: (1) rapid and, at times, noisy breathing; (2) a heart rate that seemed faster than normal; and (3) extreme irritability. The mother related that this was her first child and that the birth had been perfectly normal. The family history was noncontributory. According to the mother, the infant was never blue. The patient took her feedings well but cried a great deal, in fact almost constantly, and for no apparent reason.

Physical examination revealed a well-developed and very well-nourished 8-month-old infant. There was moderate cyanosis. No dyspnea was evident. The respiratory rate was 24 per minute. The pulse rate ranged between 100 and 120 per minute. The lungs were clear to percussion and auscultation. Examination of the heart revealed a diffuse heaving impulse over the precordium. The apex impulse was in the fifth intercostal space at the left anterior axillary line. A systolic thrill was palpable over the pulmonic area. Auscultation revealed the presence of a loud, harsh, high-pitched systolic murmur, most intense in the second and third intercostal spaces to the left of the sternum, and transmitted to the left axilla and back. There was no clubbing of the fingers or toes.

A roentgenogram of the chest, taken when the child was 8 months old, revealed a marked increase in all cardiac measurements and an especially prominent pulmonary conus (Fig. 1).

An electrocardiogram, also taken at 8 months of age, showed sinoauricular tachycardia, a rate of 150 per minute, abnormally high P waves in all leads, very deeply inverted T waves in Leads II, III, and IVF, increased amplitude of QRS complexes, and a very marked right axis deviation (Fig. 2).

Clinical Course.—The infant was seen by us at various intervals and presented no change until she was 10 months of age. At this time the mother stated that she cried constantly, would not take her feedings, and vomited frequently. The infant now showed moderate edema of the upper eyelids and the cyanosis was more marked. There was dilatation of the external

Received for publication Feb. 24, 1945.

jugular veins in the neck. The liver was enlarged and tender, its edge being palpable 3 finger-breadths below the right costal margin. The spleen was not enlarged. In spite of all therapeutic measures her course continued downhill. Edema soon appeared on the ankles and there was evidence of fluid accumulating in the abdomen. Two weeks before death a few moist râles appeared at both lung bases. The respirations gradually became more and more labored, and the cyanosis was more intense. At the age of 11 months, after suffering from right-sided heart failure for five weeks, the infant expired.

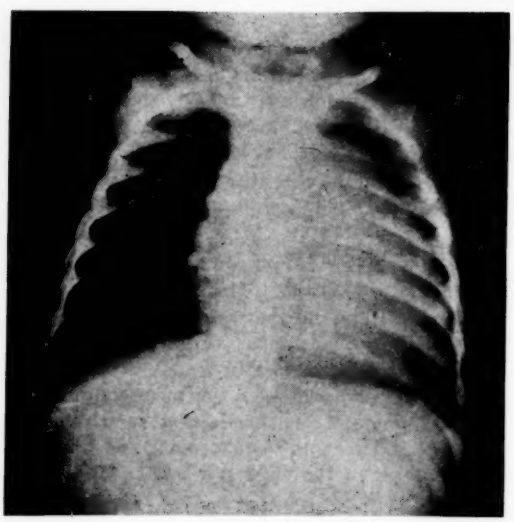


Fig. 1.

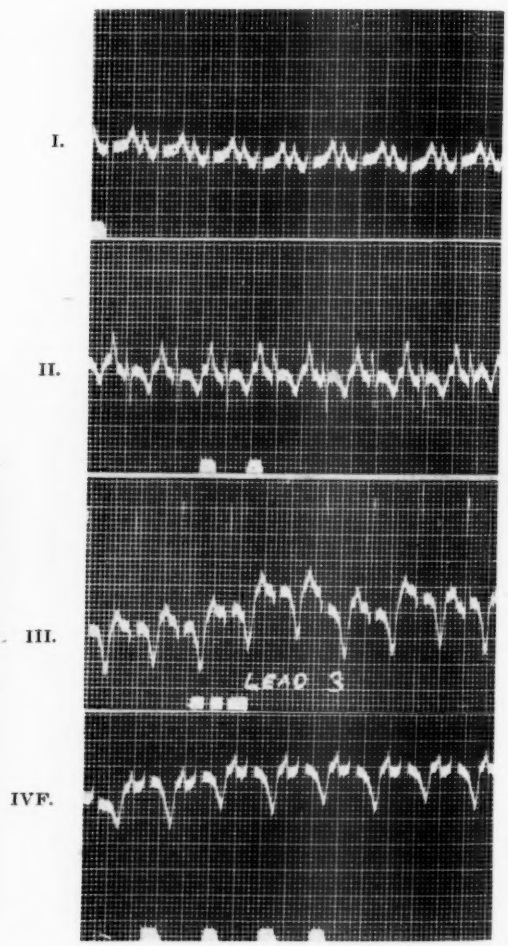


Fig. 2.

Fig. 1.—Roentgenogram taken at the age of 8 months. Note the generalized cardiac enlargement and the prominent pulmonary conus.

Fig. 2.—Electrocardiogram made at age of 8 months. Note the unusually high P waves indicating auricular enlargement; the marked right axis deviation and inverted T waves in Leads II and III indicating an enlarged right ventricle; and the high-voltage QRS complexes which are usually associated with increased mass of cardiac muscle.

Pertinent Autopsy Observations.—The pleural cavity contained a small amount of straw-colored fluid. The thymus was not enlarged. The lungs were voluminous and showed marked congestion throughout. There were no areas of consolidation. The heart (Fig. 3, *A*) weighed 102 grams (average normal for age: about 30 grams). The right auricle was greatly hypertrophied and dilated and measured 7 cm. in diameter. It had a smooth endo-

C.

B.

A.

Fig. 3.—Note the enlarged right auricle and right ventricle in *A* and the greatly thickened myocardium in *B*. The pin-point opening in the pulmonary valve with its fused leaflets is demonstrated in *C*.

cardium. The foramen ovale was not patent. The tricuspid valve had a circumference of 3.5 cm., and its cusps were smooth and glistening. The wall of the right ventricle was greatly hypertrophied (Fig. 3, *B*), its thickness measuring 1.5 cm. at the base. There was no interventricular septal defect. The pulmonary artery was found anterior to the aorta. The pulmonary valve showed complete fusion of its leaflets with only a pin-point perforation at the point of union (Fig. 3, *C*). This opening was only 2 mm. in diameter. The endocardial surface was smooth and glistening. The pulmonary artery was dilated for a distance of 2 cm. above the valve. The left auricle was small, measuring 2 cm. in diameter. The mitral valve had a circumference of 2.5 cm. and its cusps were smooth. The endocardium of the left ventricle was also smooth and glistening. The wall of the left ventricle measured 1 cm. at the base. The aortic valve showed no abnormalities and measured 2.5 cm. in diameter. The ductus arteriosus was not patent.

DISCUSSION

The most interesting feature of this case was the unusually small opening in the pulmonary valve which measured only 2 mm. in diameter. Such a small opening seems hardly compatible with life, especially when there was no other congenital defect through which the blood could be shunted. Yet this patient lived to be 11 months old and finally died of chronic right-sided heart failure which became clinically evident one month previously. The electrocardiogram and roentgenogram revealed corroborative evidence pointing to a heart in which the right cardiac chambers were preponderant. The tremendous effort required to force the blood through the narrow pulmonary opening was manifested by the great hypertrophy of the right ventricle. The mechanism involved in producing the hypertrophied right auricle is also clear; evidently it was caused by the increased work required to force blood into the ventricle which was already partially filled with blood. There was no evidence of any acute or chronic inflammatory reaction in the myocardium or endocardium, and the cause of fusion of the pulmonary leaflets has no rational explanation.

SUMMARY

A case of congenital pulmonary stenosis, with no other associated congenital defects of the heart, is reported. Death was caused by chronic right-sided heart failure at the age of 11 months.

REFERENCES

1. Gibson, S., and Clifton, W. M.: Congenital Heart Disease, Am. J. Dis. Child. 55: 761, 1938.
2. Abbott, Maude E.: Atlas of Congenital Cardiac Disease, New York, 1936, Am. Heart Association.
3. Bauer, D. DeF., and Astbury, E. C.: Congenital Cardiac Disease, Bibliography of the 1000 Cases Analyzed in Maude Abbott's Atlas, AM. HEART J. 27: 688, 1944.

MYXOMA OF HEART

W. O. Brown, M.D.
Houston, Texas

PRIMARY myxoma of the heart is of sufficient rarity, and is associated with such diagnostic and therapeutic difficulties, that the reporting of an additional case is considered worth while.

CASE REPORT

C. C., a 35-year-old white housewife, was first seen in April, 1941, because of the sudden onset of paralysis of the left forearm. The past history and family history were irrelevant. Physical examination and neurological examination revealed nothing significant except the paralysis of the left forearm, which was of the upper motor neuron type. Laboratory findings and x-ray studies of the skull and chest revealed nothing abnormal. Physical therapy and supportive treatment resulted in some improvement.

She was admitted at intervals for the next year for study but no definite conclusions were reached. Over a period of months the paralysis improved slightly. She was last admitted Nov. 5, 1943. Her husband stated that a few hours previously she had awakened from sleep complaining of severe abdominal pain and had had an involuntary stool in bed.

On admission she seemed confused mentally. The abdomen was distended and tender in the lower quadrants. The lung fields were clear and the heart sounds were recorded as normal. The blood pressure was 110/80, the pulse was 100 per minute, and the respirations were 30 per minute. The paralysis of the left arm had not changed since the last admission.

The serology was negative. The erythrocytes numbered 4,500,000 per cubic millimeter, and the leucocytes numbered 9,200. The differential count was normal. The sedimentation rate was 27 mm. in forty-five minutes (Cutler). The spinal fluid was normal in all respects. A blood culture showed no growth at the end of twelve days.

A few days after admission the patient developed temperature elevations up to 104° F. The heart was found enlarged with the apex 13 cm. to the left of the midsternal line. A gallop rhythm was present. The heart sounds were "roughened," and there was a faint systolic murmur over the mitral area. Moist râles appeared in the lung bases with findings consistent with a hypostatic bronchopneumonia. The patient rapidly became worse and died Nov. 8, 1943.

Autopsy.—The significant findings consisted of a myxoma of the left atrium and numerous infarcts, of varying ages, of the brain, spleen, kidneys, and lungs.

The heart weighed 375 grams. Arising from a narrow base just below and posterior to the old foramen ovale was a soft papillomatous grayish pink tumor 7 cm. in diameter. It was composed of soft, rubbery, translucent tissue with numerous fingerlike processes that hung suspended through the mitral orifice. In the fissures between these processes were numerous thrombi. The cut surface of the tumor had a homogenous semigelatinous appearance. Elsewhere the endocardial surfaces were smooth and glistening, and the valve leaflets thin and pliable. The mitral valve ring appeared slightly dilated, measuring 11.5 cm. in circumference. The coronary arteries and aorta appeared normal. The lower lobes of the lungs were largely collapsed and airless. Scattered through the posterior aspect of both lungs were several recent infarcts which measured up to 2 cm. in diameter. The pleural surface of the infarcts was dark and bulging and the cut surface was dark red in color and

From the Department of Pathology, Kern General Hospital, Bakersfield, California.
Received for publication April 16, 1945.

firm in consistency. The spleen weighed 275 grams, and scattered through the pulp were numerous infarcts measuring up to 2.5 cm. in diameter. These appeared of varying ages and had cut surfaces varying from a mottled yellow to a dark purplish red. The right kidney weighed 180 grams and the left weighed 220 grams. Both contained several infarcts measuring up to 3.5 cm. in diameter, some of which appeared of recent origin. The intervening parenchyma appeared normal. The brain weighed 1,350 grams. There was an irregular cortical atrophy of either parietal lobe, which was more marked on the right. There was a large area of old softening involving the operculum and the base of the precentral gyrus of the right hemisphere. This area was depressed and had a mottled yellow surface. The underlying brain substance showed softening with several small cystic cavities measuring up to 1 cm. in diameter. The blood vessels about the base appeared normal. The other organs showed nothing of significance.

Fig. 1.—Left ventricle of heart showing tumor in situ.

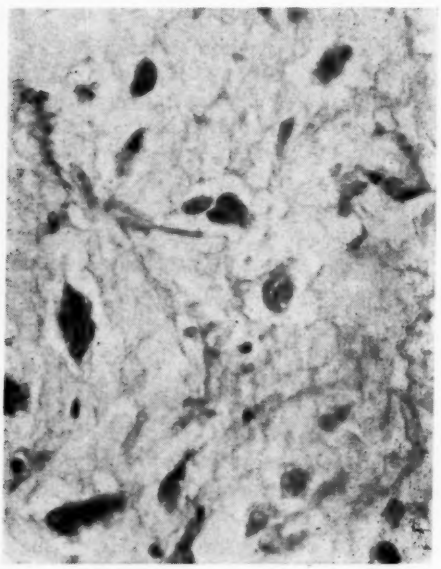


Fig. 2.—Tumor of left atrium. (×640.)

Examination of microscopic sections of the tumor of the left atrium showed it to have a relatively acellular structure composed of large stellate or polyhedral cells separated by a large amount of palely staining, faintly fibrillar or homogenous material. The cells had round, evenly chromatic nuclei and were frequently binucleated. The cytoplasm stained palely and was frequently drawn out into processes that seemed to merge with the stroma in many instances. The heart itself appeared normal. The old area of softening of the right cerebral hemisphere contained areas which had undergone liquefaction. These were surrounded by a zone of fibroblastic and glial proliferation with dense focal collections of gitter cells filled with ingested lipoid material. Parts of the area were impregnated with old blood pigment, and the blood vessels of the vicinity had prominent cuffs of gitter cells. Scattered through both hemispheres were other minute scars having a similar structure, and interpreted as being on a similar basis. Sections of the lungs, spleen, and kidneys showed the usual changes of infarction. The other organs showed nothing of significance.

COMMENT

It is surprising that such a lesion as an intracardiac tumor of the size described here should not be associated with more obvious physical findings referable

to the heart. However, that such a state of affairs is not unusual with cardiac tumors is shown by previous contributions to the literature.[1, 2] It should be noted, however, that the embolic phenomena which provided the only objective findings in the case reported here were not encountered in most of the other cases in the literature.[3] That there was some interference with normal cardiac function might be inferred from the conspicuous cardiac hypertrophy, after allowing for the weight of the tumor, in the absence of hypertension, organic valvular disease, or arteriosclerotic changes. The sudden attack of abdominal pain which brought her to the hospital the last time might be explained by a sudden ischemia of a portion of the gut by an embolus which was too small to result in infarction, or which momentarily occluded the mouth of one of the mesenteric arteries, only to be carried on in the aorta to produce one of the renal infarcts.

While other types of tumors have been reported to arise in the heart,[4, 5] myxomas account for the majority of primary benign tumors of the hearts of adults. Although other parts of the heart have been mentioned as the primary site, these tumors show a propensity for involvement of the left atrium, frequently in the region of the old foramen ovale,[6] and, except for individual variations, present, a typical structure.[7, 8]

Thorel[9] has objected to the majority of reported primary myxomas of the heart and believes that they are organizing thrombi.* There has been a notable tendency on the part of most of the authors of subsequent reports to accept metaplasia in an organizing thrombus as the probable pathogenesis of the tumors in their cases.[12] It seems germane to the question to remember that a myxoma is a specific oncologic entity and its normal tissue homologue is a differentiated but poorly specialized tissue. There seems to be no basis for assuming that repair processes such as organizing thrombi should give rise to myxomas within the cardiac chambers and not in the peripheral vessels, where most thrombi occur. The author has been unable to find any evidence indicating that thrombi in peripheral vessels ever terminate in myxomas. The cardiac ventricles, which are frequently the seat of thrombi, are practically never the site of myxomas. Moreover, the histologic structure of both myxomas and organizing thrombi should obviate confusing them.[13, 14]

The occurrence of a fibromyxosarcoma and ulcerated lesions in the pulmonary artery led Haythorn and his co-workers,[10] to postulate a probable origin of the tumor in their case from neoplastic changes originating in an organizing thrombus which developed over an atheromatous ulcer. Although thrombi do form over atheromatous ulcers, when encountered at autopsy they frequently appear recent, as though they had developed in the slowing circulation incident to the moribund state. The older ones commonly show central degeneration and liquefaction without any conspicuous attempt at organization.

It should be remembered that interference with the nutrition of the tissues, through the alterations characterizing atheromatosis, is a principal factor

*Ravid and Sachs,[5] in calling attention to an error by Haythorn, Ray, and Wolff,[10] quote Thorel[9] as considering Bachmeister's case[11] to be "an edematous ball thrombus" instead of a true tumor. Such a reference cannot be found in Thorel's article, and actually Bachmeister's case came to necropsy two years after Thorel's article appeared in the literature.

underlying the production of an atheromatous ulcer. It seems questionable whether or not tissue so affected could support an active proliferative process. Finally, the occurrence of myxomas in otherwise normal hearts, in which there is no basis for assuming a pre-existing thrombus as in the case reported here, is additional evidence that cardiac myxomas are probably associated with thrombotic processes only as coincidental phenomena.

SUMMARY

The occurrence of a myxoma of the left atrium of the heart is reported. Embolic phenomena which have been rarely encountered in previously reported cases were most prominent in the clinical picture of this case. An attempt is made to evaluate the role of organizing thrombi in the pathogenesis of cardiac myxomas. The conclusion is they play little if any part in the development of such tumors.

REFERENCES

1. Doane, Joseph C., and Pressman, Robert: Ante-Mortem Diagnosis of Tumors of the Heart, Am. J. M. Sc. 203: 520, 1942.
2. Lisa, James R., Hirschorn, Louis, and Hart, Crawford A.: Tumors of the Heart, Arch. Int. Med. 67: 91, 1941.
3. Beck, Claude S.: An Intrapericardial Teratoma and a Tumor of the Heart; Both Removed Operatively, Ann. Surg. 116: 161, 1942.
4. Maun, Mark E. Polypoid Thrombus of the Left Auricle, With Report of a Case, AM. HEART J. 26: 549, 1943.
5. Ravid, J. M., and Sachs, Jacob: Tumors of the Heart, AM. HEART J. 26: 385, 1943.
6. Hamilton-Paterson, J. L., and Castleden, L. I. M.: Intracardiac Tumors, Brit. Heart J. 4: 103, 1942.
7. Dexter, R., and Work, J. L.: Myxoma of the Heart, Arch. Path. 32: 995, 1941.
8. Orr, John W.: Endothelioma (Pseudomyxoma) of the Heart, J. Path. & Bact. 54: 125, 1942.
9. Thorel, Ch.: Pathologie der Kreislauforgane, Ergebn. d. allg. Path. u. Anat. 9: 901, 1903.
10. Haythorn, Samuel R., Ray, W. B., and Wolff, Regis A.: Primary Fibromyxosarcomas of the Heart and Pulmonary Artery, Am. J. Path. 17: 261, 1941.
11. Bachmeister: Zur Kasuistik der Primaren Herzgeschwulste, Centralbl. f. allg. Path. u. path. Anat. 17: 257, 1906.
12. Warthin, A. S.: Myxoma-Like Growths in the Heart, Due to Localizations of Spirochaeta Pallida, J. Infect. Dis. 19: 138, 1916.
13. Fawcett, R. E. M., and Ward, E. Milford: Cardiac Myxoma, Brit. Heart J. 1: 249, 1939.
14. Ewing, James: Neoplastic Diseases, ed. 4, Philadelphia, 1940, W. B. Saunders Co., pp. 187-188.

Letters

To the Editor:

My experience in over one hundred thousand examinations of the hearts of Merchant Seamen in a two and one-half year period is not in complete accord with the conclusions stated by Niehaus and Wright in their article, "Facts and Fallacies About the Normal Apex Beat," in the December, 1945, issue of the AMERICAN HEART JOURNAL.

The normal apex beat is seen in a minority of examinees at rest. The number may be increased by a lateral view in a good light.

The normal apex beat may be palpated in a majority of men without exercise. Contrary to the usual description of the apex beat, it is more often a subtle slight movement of a small area of the precordium than a definite thrust. The more sensitive the hand of the examiner, the more apex beats will be felt.

When examinees are subjected to a short period of exercise, and their precordia are palpated with the men bending forward and at the end of forced expiration, well over 90 per cent of apex beats may be palpated and a large number may be seen with the same technique.

The accuracy of these observations was tested by chest x-ray of every man and fluoroscopy of the doubtful cases. Percussion was a valuable though static and indirect check on the position of the apex beat.

Difficulty in palpating an apex beat was usually due to obesity or a thick chest wall in normal men, and occasionally in abnormal men to a flabby systole in a dilated heart. The effect of age on the apex beat was not evaluated.

(Signed)
EDWIN QUINN
P.A. Surg. (R) U.S.P.H.S.

162 Navy Walk
Fort Greene Houses
Brooklyn 1, N. Y.
Feb. 14, 1946

To the Editor:

It is to be regretted that Dr. Quinn did not have his clinical assistants record his observation at the time each of his examinations was made. Such a record would have been formidable. He undoubtedly would have found that a critical analysis of his recorded facts of the "subtle slight movement of a small area of the precordium" could not have been identified in the majority of instances as a reliable first rate physical sign, even with a "more sensitive hand."

Physical diagnosticians differentiate between "an apex beat" and an "apex thrust." We must insist, however, that an apex beat has definite features, which are not too elusive.

Dr. Quinn's observation that the apex beat can be made more apparent by exercise, by bending forward, and by palpating at the end of the expiration seems valuable. However, this is not the usual method followed in eliciting this physical sign. In examining large groups under certain conditions it is conceivable that his modified, additional method would be valuable.

(Signed)
FREDERICK W. NIEHAUS, M.D.
WILLIS D. WRIGHT, M.D.

1622 Medical Arts Building
Omaha 2, Neb.
March 5, 1946

Abstracts and Reviews

Selected Abstracts

Allen-Williams, G. M.: Pulse Rate and Blood Pressure in Infancy and Early Childhood. Arch. Dis. Childhood **20**: 125 (Sept.) 1945.

An investigation of anthropometric methods which was carried out in municipal day nurseries at Oxford offered an opportunity for studying under standard conditions, the resting pulse rate and the ranges of blood pressure in healthy children, aged 6 months to 5 years.

The pulse rates were taken daily for a week during the afternoon rest hour when the children had been sleeping soundly for some time. The mean pulse rate per minute in children aged 6 to 12 months was 122 for males and 109 for females; in children aged 1 to 2 years it was 109 and 110, respectively. At 2 to 3 years of age the pulse rate fell to 100 among males and remained at this level up to 5 years of age. The mean pulse rate among females was found to decline regularly after they reached the age of 1 year, and at 4 to 5 years it was the same in both sexes. It was noted that there is a greater variation in the sleeping pulse rates of children in the same age group than there is in the daily sleeping pulse rate of the individual child.

Blood pressure was recorded very carefully from the right arm during the morning and only when the child was quiet and cooperative. The cuff had a width of 4 cm. for children under 2 years of age, 6 cm. for children 2 to 4 years of age, and 8 cm. for children 4 to 5 years of age. The mean blood pressures for males and females, respectively, were: at 6 to 12 months, 88/59 and 92/62; at 1 to 2 years, 96/66 and 95/65; at 2 to 3 years, 98/63 and 92/60; at 3 to 4 years, 99/66 and 99/64; and at 4 to 5 years, 99/65 and 99/66. There was an apparent tendency for systolic blood pressure to increase with age up to 4 years of age and to decline between 4 and 5 years of age. There was found to be a high correlation between the systolic and diastolic pressures, but no significant correlation between blood pressure and body weight in childhood. The author believes that his observations suggest a physiologic change in the circulatory system of children at the age of 2 to 3 years.

LAPLACE.

Burrows, A., and Stokes, W.: Mercurial Diuretics. Intolerance as Shown by Skin Sensitivity. Brit. Heart J. **7**: 161 (Oct.) 1945.

Nine cases are reported in which skin erythema followed the administration of mercurial diuretics. Patch tests were made in all cases; this test is recommended as useful in determining the presence of sensitivity of the skin, especially when accumulation of the drug is suspected or when continuation of treatment is desirable after cutaneous sensitization.

The authors point out that many patients with sustained high dosage of mercurial diuretics show no signs of intolerance. Sensitization, idiosyncrasy, or allergy may be of different degrees. Skin rashes and itching, without other complications, would seem to indicate moderate sensitivity. There appears to be a threshold concentration of mercury in the blood, above which signs of allergy develop. This threshold may vary with the individual patient. Excessive dosage, poor diuresis, and renal impairment favor accumulation of the drug. The occurrence of cutaneous complications does not preclude further use of mercurial diuretics in adjusted dosage once the phase of sensitization is past. LAPLACE.

Evans, W., and Lewes, D.: The Carotid Shudder. Brit. Heart J. 7: 171 (Oct.) 1945.

In nine patients in whom subsequent clinical, cardiographic, and cardioscopic examination established the presence of aortic stenosis and incompetence, the authors noted a characteristic sign which by itself permitted a diagnosis of the combined aortic lesion from inspection of the neck. This sign consisted of a momentary quiver or vibration which occurred at the height of the carotid pulse and was named the "carotid shudder." It is not found in all cases of aortic incompetence and stenosis but its presence is a sure indication of the dual lesion. LAPLACE.

Cottrell, J. D., and Hayward, G. W.: The Effects of Emetine on the Heart. Brit. Heart J. 7: 169 (Oct.) 1945.

Changes in the electrocardiogram, blood pressure, and pulse rate produced by emetine and emetine bismuth iodide have been studied in soldiers under treatment for amebiosis. All were otherwise healthy, and the initial electrocardiograms were normal. Diminution or inversion of the T waves occurred in one or more leads in 25 of 32 patients receiving emetine and in 12 there was an increase in the P-R interval of from 0.02 to 0.04 second. Similar changes occurred during treatment with emetine bismuth iodide; seven of eight cases showed diminution in T waves and prolongation of the P-R interval. The cardiogram returned to normal eight to twelve days after completion of treatment. The effect on the blood pressure and pulse rate of both drugs was insignificant, and in no case was there any clinical evidence of myocardial insufficiency. LAPLACE.

Gregory, R., and Levin, W. C.: Studies in Hypertension. V. Effect of High Spinal Anesthesia on the Blood Pressure of Patients With Hypertension and Far-Advanced Renal Disease—Its Possible Relationship to the Pathogenesis of Hypertension. J. Lab. & Clin. Med. 30: 1037 (Dec.) 1945.

Observations were made on the blood pressure changes produced by high spinal anesthesia in cases of hypertension with far-advanced renal disease. The study was dictated by the authors' belief that the elevated blood pressure of hypertensive patients with far-advanced renal arteriolar disease would not fall as much under spinal anesthesia as would the blood pressure of patients with hypertension and normal renal function under the same conditions if the initial blood pressure elevation were due to a humoral substance produced in the kidney. Twelve hypertensive patients with uremia, ten having essential hypertension, one acute glomerulonephritis, and one chronic glomerulonephritis, were studied. Their fall of blood pressure during spinal anesthesia was equal to that similarly produced in patients with essential hypertension and normal renal function. This result is considered evidence that even in patients with extreme irreversible arteriolar disease as shown by clinical and chemical evidence of uremia, the elevation of blood pressure is due to increased vasomotor tonus. LAPLACE.

Wolf, R. E., Rauh, L. W., and Lyon, R. A.: The Prevention of Rheumatic Recurrences in Children by the Use of Sulfathiazole and Sulfadiazine. J. Pediat. 27: 516 (Dec.) 1945.

The authors report their experience with the effectiveness and reactions of sulfathiazole and sulfadiazine employed in groups of rheumatic children during the period of 1943 to 1945. The dosage used was sulfathiazole 0.5 Gm. twice daily or sulfadiazine 0.5 Gm. once daily.

There were no recurrences of rheumatic fever during treatment in a group of 70 children who received the drugs for a total of 81 patient seasons. One child developed subacute bacterial endocarditis while being treated and another developed it during the summer between treatment periods. One child developed rheumatic fever at the latter time. A few mild reactions occurred in the form of albuminuria, leucopenia, and skin rashes. These occasionally appeared as late as five months after inauguration of treatment. On the basis of this study, it appeared that this type of prophylactic therapy is safe and effective but should be con-

tinued throughout the year and sometimes for two years. The patient should have completely recovered from his infection before prophylactic treatment is started. LAPLACE.

Hines, L. E., and Kessler, D. L.: Ineffectiveness of Penicillin in Some Cases of Bacterial Endocarditis. Quart. Bull., Northwestern Univ. M. School **19**: 296 (Winter Quart.) 1945.

There are many causes for the ineffectiveness of penicillin in the treatment of subacute bacterial endocarditis. The patient may die of valvular heart disease in the same manner as a patient who had never acquired bacterial endocarditis. Pathologic and clinical variations such as mycotic aneurysms, nephritis, myocarditis, cerebral embolism, and pulmonary infarction may be critical complications. Inadequate dosage of penicillin is often a cause of failure, especially in the presence of relatively insensitive organisms. Finally, penicillin itself may be harmful; practically no serious toxic effects have been reported, but allergic reactions are not rare. LAPLACE.

Naide, M., Sayen, A., and Comroe, B. I.: Characteristic Vascular Pattern in Patients With Rheumatoid Arthritis. Arch. Int. Med. **76**: 139 (Sept.) 1945.

The basal vascular tone of a group of patients with rheumatoid arthritis was found to be high when studied by means of a test used for grading vascular tone. The test employed involved determination of the degree of vasoconstriction and vasodilatation as reflected in temperatures of the fingers and toes during a cool period and during the application of moderate heat to the trunk in a constant-temperature room at 20° C.

The high grade of vascular tone was present in the unaffected or the less affected digits or extremities so that this type of vascular response appears to be characteristic of individuals who develop rheumatoid arthritis. The tendency for the peripheral vessels in these patients to constrict easily may be one of the basic factors in predisposing them to rheumatoid arthritis and to flare-ups of the condition after emotional upsets and exposure to cold.

Subjects with early rheumatoid arthritis may have a dissociated type of temperature response to cold and reflex heat in their digital vessels which permits early diagnosis of the condition in some patients. NAIDE.

Gross, R. E.: Surgical Correction for Coarctation of the Aorta. Surgery **18**: 673 (Dec.) 1945.

The author operated upon two patients with coarctation of the aorta following demonstration in dogs of the feasibility of removing segments of the thoracic aorta and re-establishing the arterial channel by end-to-end sutures of the vessel. In each of the two cases reported, the narrowed and obstructed part of the aorta was resected and the continuity of the vessel was then re-established. In both patients the anastomosis was satisfactorily completed but in the first patient, a 5-year-old boy, quick removal of the clamps resulted in the sudden opening of a huge vascular bed with immediate cardiac dilatation and death. In the second patient, a 12-year-old girl, the aortic clamps were removed very slowly over a period of ten minutes so that the cardiac and circulatory readjustments were brought about more gradually. In this patient, who survived, the pressure and pulsations in the lower extremities returned gradually until they were fairly normal by the seventeenth postoperative day. There was a concomitant decrease of the hypertension which had previously existed in the arms and upper portion of the body. NAIDE.

Tyson, M. D., and Goodlett, W. C.: Venous Pressures in Disorders of the Venous System of the Lower Extremities. Surgery **18**: 669 (Dec.) 1945.

The authors measured the venous pressure in the lower extremities of patients with thrombophlebitis of leg veins. The normal venous pressure at the ankle with the patient

in the supine position and the table tilted so that the anterior surface of the foot was level with the auricles was found to be 2 to 9 cm. of water. When the femoral vein was occluded by a blood clot, the venous pressure at the ankle was elevated. In one such patient the venous pressure at the ankle of the affected leg was 49 cm., whereas on the unaffected side the venous pressure was 2 centimeters. Following ligation of the femoral vein the venous pressure at the ankle was 60.5 centimeters. In several of the patients, the high venous pressure declined gradually following femoral ligation as collateral circulation improved. The fall in venous pressure was attended by a corresponding reduction of edema. NAIDE.

Member, S., and Bruger, M.: Experimental Arteriosclerosis. VIII. The Effect of Feeding Olive Oil on the Absorption and Deposition of Cholesterol. Arch. Path. 40: 373 (Nov.-Dec.) 1945.

The authors found that when olive oil was added to the diet of rabbits in addition to cholesterol, the levels of blood cholesterol were slightly higher than when cholesterol was added alone. The deposition of cholesterol in the liver and the aorta was decidedly greater with the combination of olive oil and cholesterol than with cholesterol alone. NAIDE.

Grossman, C. M.: Pneumococcal Pericarditis Treated With Intrapericardial Penicillin, New England J. Med. 233: 689 (Dec. 6) 1945.

A case of pneumococcal pericarditis caused by Type VIII pneumococcus is reported. The patient was a man, aged 30 years, who was treated with penicillin which was administered parenterally and by intrapericardial injection. The first intrapericardial injection of penicillin consisted of 20,000 Oxford units. A second intrapericardial injection of 15,000 units was made thirty-six hours later. Recovery was uneventful. Although the intrapericardial administration of penicillin was not regarded as unquestionably responsible for the cure, the author believes that this procedure is warranted by the fact that the treatment of pleural and synovial infection is more successful when penicillin is used locally in addition to the parenteral route.

BELLET.

Crafoord, C., and Nylin, G.: Congenital Coarctation of the Aorta and Its Surgical Treatment. J. Thoracic Surg. 14: 347 (Oct.) 1945.

Two cases of coarctation of the aorta are reported in which surgical treatment was employed successfully. The patients were aged 12 and 27 years. The operation consisted of resection of the constricted part of the aorta and suture of the proximal and distal portions. The first operation was performed on Oct. 19, 1944, and the second on Oct. 31, 1944. Convalescence was uncomplicated in both cases. The patients were re-examined in March, 1945, and at that time were in excellent health and had returned to their former duties. Hypertension had been replaced by normal blood pressure. The blood pressure in the legs had likewise returned within the normal range.

The authors regard the operative results in these cases as evidence in favor of the mechanical theory of the cause of hypertension associated with coarctation of the aorta.

BELLET.

Wedd, A. M., and Blair, H. A.: The Action of Acetylcholine and Epinephrine on the Turtle Ventricle. Am. J. Physiol. 145: 147 (Dec.) 1945.

The action of acetylcholine on the turtle heart was investigated because in earlier work the refractory period was determined by a faulty method. The effect of acetylcholine on contractility was observed on ventricular strips suspended in a bath and stimulated rhythmically, the refractory period being determined from the Q-T interval of the electrocardiogram. Contraction height and diastolic length were decreased and the refractory period was slightly shortened. This action required much higher concentrations than those needed to produce the so-called inhibitory effects and was offset by atropine. It was believed to represent a direct action on myocardial fibers. The response to carbaminoylcholine ("Doryl") was found to be similar to that of acetylcholine.

The action of epinephrine on ventricular strips was studied in a similar manner. The results were strikingly irregular. The mechanically recorded contractions were at times increased and at other times decreased. The effect on the electrical responses of strips was likewise irregular, making it difficult to say that epinephrine has any definite influence on refractory period or conduction. LAPLACE.

Haney, H. F., and Lindgren, A. J.: The Effect of Acetylcholine on the Atropinized Denervated Heart. Am. J. Physiol. **145**: 177 (Dec.) 1945.

This investigation concerns the possibility that acetylcholine exerts a direct stimulatory action on heart tissues or on ganglion cells within the heart, an action which is independent of and in opposition to its cardiodepressor influence. Dogs were subjected to removal of the stellate and upper five or six thoracic sympathetic ganglia and section of both vagus nerves. In three dogs, the adrenals were demedullated or denervated. At the beginning of each experiment, atropine sulfate, 2.6 mg. was given intravenously. The dogs were trained to lie quietly during the experiments. Acetylcholine was administered by venous infusion in doses of 1 to 4 mg. while the heart rate was recorded by means of the electrocardiogram. In 21 of 25 experiments on eight dogs, the heart rate increased more than 11 beats per minute with a maximum of 238 beats per minute. The time interval between the injection of acetylcholine and the onset of tachycardia was four to seven seconds. The brevity of this time interval is evidence in favor of the existence of a direct stimulatory action by acetylcholine either on the atropinized heart tissue or on intracardiac ganglion cells having a cardioaccelerator function. LAPLACE.

Ralston, H. J., Collings, W. D., Taylor, A. N., and Ogden, E.: Venous Return in the Absence of Cardiac Drive. Am. J. Physiol. **145**: 441 (Jan.) 1946.

Venous return in the absence of cardiac drive has never been fully explained. Skeletal muscle tone has been regarded as an important factor. The phenomenon was therefore studied in acute experiments on dogs and cats by clamping the aorta and pulmonary artery and measuring the amount of blood which drained from the azygos vein. The amount of blood recovered in this procedure was 40 ml. per kilogram of body weight when light anesthesia was used, 27 ml. per kilogram of body weight when the animals were curarized, and 23 ml. per kilogram of body weight when dead animals, twenty-three minutes after experimentally induced ventricular fibrillation, was used. Control animals which were bled without arterial clamping yielded 46 ml. per kilogram of body weight. Thus a large proportion of the blood which can be drained from the azygos vein in the living animal with intact circulation can still be obtained after cardiac drive is eliminated. Splenic contraction appeared to contribute little if any blood to the total yield but skeletal muscle activity accounts, apparently, for about half the total yield. Elastic forces persistent in the tissues even after death may account for the remainder of the blood yield. LAPLACE.

MacNeal, Ward J., Blevina, A., and Poindexter, C. A.: Clinical Arrest in Enterococcal Endocarditis. Am. J. M. Sc. **211**: 40 (Jan.) 1946.

Attention is called to the neglected recognition of *Streptococcus faecalis* as a cause of bacterial endocarditis. The authors estimate that it is the infecting organism in 10 to 15 per cent of such cases. They report the case of a man, aged 34 years, who had known valvular heart disease since 1927 and developed bacterial endocarditis late in 1943. Repeated blood cultures were positive for *Str. faecalis* and the organism was found to be rather resistant in vitro to the bacteriostatic action of neoarsphenamine, mapharsen, thiobismol, and penicillin; very resistant to sulfonamides; and quite susceptible to enterococcus bacteriophage. The patient was treated predominantly with thiobismol, penicillin, and bacteriophage for a period of nine months, followed by continued treatment with bacteriophage. The disease appears to have been arrested for a period of over a year. LAPLACE.

Gubner, R., Silvertone, F., and Ungerleider, H. E.: Range of Blood Pressure in Hypertension. J. A. M. A. **130:** 325 (Feb. 9) 1946.

The current status of pressor and depressor tests in hypertension is reviewed, together with present concepts of the etiology of hypertension. The importance of knowing the maximum and minimum range of the blood pressure is emphasized. The authors recommend breath-holding or brief inhalation of spirit of ammonia as the most satisfactory method of obtaining the maximum pressor level, and hyperventilation combined with carotid pressure for obtaining the basal depressor level. Employment of these procedures makes it possible to differentiate humoral and neurogenic components in cases of hypertension. The authors believe that the neurogenic or vasomotor component is the important determinant in the initial elevation in blood pressure. In later stages, as the result of renal arteriolosclerosis and ischemia, the renal pressor mechanism becomes involved. In older age groups arteriosclerosis of the medullary vessels with ischemia of the vasomotor system may be a contributing factor in heightened vasomotor pressor activity and hypertension. NAIDE.

Cardozo, E. L., and Eggink, P.: Circulation Failure in Hunger Edema. Canad. M. A. J. **54:** 145 (Feb.) 1946.

The circulation was studied in 29 cases of severe malnutrition. Characteristic features were a slow pulse rate, ranging from 40 to 50 per minute, a low blood pressure with systolic levels under 100 mm., and a low pulse pressure. The circulation time (using 10 per cent magnesium sulfate) was prolonged; in 76 per cent of the patients it was more than 20 seconds and in the more serious cases it was more than 30 seconds. The circulation time was increased in the absence of apparent evidence of heart failure. The electrocardiograms showed low voltage and bradycardia. Roentgenography failed to reveal evidence of any cardiac enlargement. The basal metabolic rate ranged from -20 to -40 per cent. The serum protein level was low, particularly the albumin fraction. The hemoglobin averged between 60 and 70 per cent. BELLET.

Logue, R. B., and Hanson, J. F.: Electrocardiographic Changes Following Heat Stroke. Ann. Int. Med. **24:** 123 (Jan.) 1946.

A case is reported in which significant electrocardiographic changes occurred during heat stroke. The authors found relatively few similar reports in the literature, although the cardiac complications of heat stroke have been generally recognized and consist of dilatation of the right ventricle and subendocardial hemorrhages. In experimental heat stroke, various arrhythmias have been produced. In the present case, the electrocardiographic changes consisted of inversion of the T waves in all leads, with slight S-T segment deviation. These changes disappeared during a period of two and one-half months. It is pointed out that the cause of the electrocardiographic changes is uncertain, since the patient was in profound shock and digitalis had been administered for twenty-four hours prior to the first electrocardiogram. BELLET.

Loewe, L., Plummer, N., Niven, C. F., Sherman, J. M.: Streptococcus s.b.e. in Subacute Bacterial Endocarditis. J. A. M. A. **130:** 257 (Feb. 2) 1946.

An apparently new variety of nonhemolytic streptococcus was isolated in 41 (39 per cent) of a series of 106 consecutive blood cultures from cases of subacute bacterial endocarditis. The organism was designated *Streptococcus s.b.e.* Its cultural properties, relationship to other streptococci, and serologic classification were studied in detail. Its refractory character was strikingly apparent from a comparative study of treatment statistics, recovery percentage, mortality rate, and incidence of recurrence. Intensive, massive penicillin treatment was found to be mandatory in order to terminate the disease in patients affected with *Streptococcus s.b.e.* The optimum dosage of penicillin was an uninterrupted span of treat-

ment for eight weeks with daily intravenous administration of at least 2 million Oxford units. The prompt identification of this organism as the causative agent in subacute bacterial endocarditis facilitated by the use of the presently available diagnostic serum has been a lifesaving measure. BELLET.

Smolik, E., Blattner, R. J., and Hays, F. M.: Brain Abscess With Congenital Heart Disease. J. A. M. A. 430: 145 (Jan. 19) 1946.

The authors regard the association of brain abscess with congenital heart disease as being insufficiently emphasized in the literature and report a case of this type. The patient was a girl, aged 9 years, whose cardiac lesion was either a patent ductus arteriosus or an interventricular septal defect. Symptoms suggestive of brain abscess developed and the diagnosis was established by ventriculography. Surgical drainage of the abscess was followed by complete recovery. Penicillin and sulfonamide therapy were maintained during convalescence. The organism cultured from the aspirated pus was identified as a member of the *Haemophilus influenzae* group.

It is pointed out that the ante-mortem diagnosis of brain abscess in patients with congenital heart disease is uncommon and that the diagnosis could be made more frequently if the possibility of this association is borne in mind. BELLET.

Robertson, H. F., Schmidt, R. E., and Feiring, W.: The Therapeutic Value of Early Physical Activity in Rheumatic Fever, Preliminary Report. Am. J. M. Sc. 211: 67 (Jan.) 1946.

Confinement to bed is not regarded by the authors as necessarily affording optimum rest, especially in cases of acute rheumatic fever where prolonged confinement tends to produce restlessness and to develop a psychoneurosis. The therapeutic value of early ambulation in rheumatic fever was therefore studied in a series of two hundred cases. The patients were placed on a regime in which comfort was the sole factor in determining the extent of permitted activity. All patients except those who had heart failure or incapacitating joint inflammation were allowed to use the latrine during the first twenty-four hours, and thereafter they were permitted to sit up in a chair for increasing intervals. As strength returned they were allowed to walk about the hospital. Joint discomfort very rarely prohibited ambulation for more than forty-eight hours when adequate amounts of salicylate were given. Tachycardia, cardiac murmurs, heart block, subcutaneous nodules, moderate joint pains, rapid sedimentation rates, abnormal electrocardiograms, or other laboratory findings indicative of active rheumatic fever or carditis were not used as indications for confinement.

No unfavorable effects of this treatment were noted, while, on the other hand, the advantages included marked decrease in the incidence and severity of anxiety neuroses, sounder sleep, improved bowel function, decreased abdominal pain, improved appetite, and gain in weight. In the majority of cases the manifestations of acute rheumatic fever disappeared during the period of physical activity. The success of this type of treatment invites attention to re-evaluation of the currently accepted policy of prolonged bed rest with its disadvantages in the management of acute rheumatic fever. LAPLACE.

Bloomfield, A. L., and Halpern, R. M.: The Penicillin Treatment of Subacute Bacterial Endocarditis; Some Problems. J. A. M. A. 129: 1135 (Dec. 22) 1945.

A series of eighteen consecutive cases of subacute bacterial endocarditis is reported in which penicillin therapy was employed and the infection has been arrested for periods of three to seventeen months. Bacterial and clinical arrest in 100 per cent of this series is contrasted with the arrest of only 50 to 75 per cent in the series of more briefly treated cases reported in the literature.

An important criterion for determining the dosage of penicillin necessary to obtain a favorable response was the strain sensitivity of the organism. If more than 0.1 Oxford unit of penicillin per cubic centimeter of medium was required for complete inhibition of growth,

the case was likely to be refractory to the amount of treatment usually given and doses up to 1 million Oxford units per day might be necessary.

In order to obtain the highest percentage of cures, treatment should be continued for two months and in some cases longer. If the strain is sensitive, the best treatment consists of a total daily dose of at least 200,000 units administered in four to eight intramuscular injections. In the presence of more resistant strains, very large doses of 500,000 units or more of penicillin may be necessary to obtain a cure.

Subcurative therapy may produce not only deceptive pseudocures with return of bacteriemia as soon as treatment is stopped, but also a more resistant strain of streptococci. It is important to recognize the infection early so that treatment may be started before excessive heart damage has occurred. BELLET.

Wheeler, E. O., and White, P. D.: Insomnia Due to Left Ventricular Heart Failure. J. A. M. A. **129**: 1158 (Dec. 22) 1945.

Insomnia as a presenting symptom of left ventricular failure has been generally neglected. When dyspnea is not a prominent complaint, however, insomnia may be the predominant symptom of pulmonary congestion. In such cases, the patient may be inadequately treated because of failure to recognize the underlying heart disease. Treatment with digitalis and diuretics and restriction of salt result in improvement of heart function and relief of the insomnia. BELLET.

Iokhveds, B. I.: Intracardiac Blood Transfusion. Am. Rev. Soviet Med. **3**: 116 (Jan.) 1946.

Intracardiac blood transfusion is recommended only for patients who are moribund. Two cases are reported in which the blood was introduced directly into the ventricles. The transfusions were given respectively eight and ten minutes after clinical death. In one patient the injection was made into the right ventricle and in the other patient into the left ventricle. Use of the left ventricle is preferable, particularly when the moribund state is the result of severe hemorrhage, as in one of the cases reported. Three advantages for left-sided transfusion are cited: (1) The increase in the contents of the left ventricle acts as an impulse to start contraction. (2) Even the first comparatively weak contractions of the heart partially re-establish the blood supply to the brain centers. (3) The left ventricular route immediately improves the coronary blood supply. The use of the right ventricle for transfusion has been previously reported, but the author has found no previous reference to the use of the left ventricle for this purpose. MCMILLAN.

Connell, W. F., Wharton, G. K., and Robinson, C. E.: The Relationship of Blood Pressure and Serum Thiocyanate. Am. J. M. Sc. **211**: 74 (Jan.) 1946.

The purpose of this investigation was to ascertain whether there is any correlation between the height of the blood pressure and the amount of thiocyanate in the blood serum of persons who have not received thiocyanate therapeutically. In 341 subjects whose blood pressures ranged from hypotensive levels averaging 99/61 to hypertensive levels averaging 228/131, a substance giving the color reaction of thiocyanate was found in the serum in concentrations of 0 to 2.77 mg. per 100 milliliters. No correlation was found between the serum concentration of this substance which was estimated as potassium thiocyanate, and the height of the diastolic blood pressure. It is concluded that, if thiocyanate actually does occur normally in the blood serum, it has no role in the regulation of blood pressure. LAPLACE.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. ROY W. SCOTT
President

DR. HOWARD F. WEST
Vice-President

DR. GEORGE R. HERRMANN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

*DR. EDGAR V. ALLEN Rochester, Minn.†
DR. ARLIE R. BARNES Rochester, Minn.
DR. WILLIAM H. BUNN Youngstown, Ohio
DR. CLARENCE de la CHAPELLE New York City
DR. NORMAN E. FREEMAN Philadelphia†
*DR. TINSLEY R. HARRISON Dallas
DR. GEORGE R. HERRMANN Galveston
DR. T. DUCKETT JONES Boston
DR. LOUIS N. KATZ Chicago
*DR. SAMUEL A. LEVINE Boston
DR. GILBERT MARQUARDT Chicago†
*DR. H. M. MARVIN New Haven
*DR. EDWIN P. MAYNARD, JR. Brooklyn
*DR. THOMAS M. McMILLAN Philadelphia
DR. JONATHAN MEAKINS Montreal†
DR. E. STERLING NICHOL Miami
DR. HAROLD E. B. PARDEE New York City
DR. WILLIAM B. PORTER Richmond, Va.
*DR. JOHN J. SAMPSON San Francisco†
*DR. ROY W. SCOTT Cleveland
DR. FRED M. SMITH Iowa City
DR. HOWARD B. SPRAGUE Boston†
DR. GEORGE F. STRONG Vancouver, B.C., Can.
DR. WILLIAM D. STROUD Philadelphia
DR. WILLIAM P. THOMPSON Los Angeles
DR. HARRY E. UNGERLEIDER New York City
*DR. HOWARD F. WEST Los Angeles
DR. PAUL D. WHITE Boston
DR. FRANK N. WILSON Ann Arbor
*DR. IRVING S. WRIGHT New York City†
DR. WALLACE M. YATER Washington, D. C.

*EXECUTIVE COMMITTEE
†IN MILITARY SERVICE

DR. H. M. MARVIN, *Acting Executive Secretary*
ANNA S. WRIGHT, *Office Secretary*
TELEPHONE, CIRCLE 5-8000

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.